THE JOURNAL

OF THE

American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 169, NO. 15 — CHICAGO, ILLINOIS — APRIL 11, 1959

COPYRIGHT, 1959, BY AMERICAN MEDICAL ASSOCIATION

TREATMENT OF PULMONARY EMPHYSEMA

George N. Bedell, M.D.
and
Paul M. Seebohm, M.D., Iowa City

The etiological diagnosis is of basic importance in patients with emphysema because the distinction between primary and secondary types decides the plan of treatment. The general aim of treatment is to keep the patient active, to preserve as much lung tissue as possible, and to maintain comfort. In primary emphysema, breathing exercises and such expectorants as potassium iodide are helpful, and in severe cases oxygen is indicated if used with due caution. But in secondary emphysema it may be necessary to use bronchodilators and steroids to combat underlying bronchial asthma, antibiotics to stop destructive infections, and other therapy directed at the original cause.

PULMONARY emphysema is a disease characterized pathologically by loss of elastic tissue and destruction of alveolar walls in the lung leading to the formation of enlarged air sacs. The physiological abnormalities are uneven distribution of inspired air, expiratory airway obstruction, loss of alveolar capillary surface available for diffusion, reduction in the vascular bed, and, eventually, pulmonary hypertension and cor pulmonale. For the purpose of this paper emphysema is classified as localized or generalized. The localized type of emphysema consists of one or more greatly enlarged alveoli with the rest of the lung normal. This probably is a congenital abnormality of one part of the lung. When cystic areas interfere with function by compressing normal lung tissue, they can be successfully removed. The generalized disease can be of unknown cause, or it can result from such disorders as bronchial asthma, bronchiectasis, tuberculosis, silicosis, and other types of chronic lung disease. Most of this discussion concerns the generalized form of the disease.

In the treatment of the patient with emphysema it is extremely important to establish the etiology of the emphysema. If it is secondary to bronchial asthma the treatment is primarily the treatment of bronchial asthma. Many physicians fail to make a clear distinction between bronchial asthma with emphysema and emphysema with chronic bronchitis. The disease in the patient with bronchial asthma and emphysema usually starts with attacks of paroxysmal dyspnea, frequently at night. The patient with primary emphysema early in his ill-

From the Pulmonary Research Laboratory, Cardiovascular Research Laboratories, Department of Internal Medicine, College of Medicine, State University of Iowa.

Read before the Clinical Meeting of the American Medical Association, Minneapolis, Dec. 5, 1958.

ness has dyspnea only with exertion, so his sleep is not interrupted. The patient with bronchial asthma and emphysema may have rhinitis and nasal polyps, sinusitis, and eosinophilia. The patient with emphysema and chronic bronchitis usually does not. The chest roentgenogram in both is similar, showing hyperaeration. Pulmonary function tests may not make a distinction between the two disorders; the patient with primary asthma and secondary emphysema may show improvement in vital capacity, maximal breathing capacity, and maximal flow rates after the administration of epinephrine (Adrenalin), whereas the patient with primary emphysema has a minimal or slight response. Bates [1] has reported good results in making the differentiation on the basis of diffusion, which should be normal in patients with bronchial asthma and reduced in patients with emphysema. When the asthmatic patient develops secondary emphysema, however, this test loses its value in distinguishing between these two disorders. The patient with bronchial asthma responds well to steroid therapy, whereas the patient with primary emphysema responds poorly. We believe that good response to steroid therapy in patients with pulmonary emphysema is reported because of a poor distinction between the patient with bronchial asthma and emphysema and the patient with primary emphysema. Those with bronchial asthma almost invariably improve with steroid therapy.

Aims of Treatment

Let us direct our attention to treatment of the emphysema itself. In the patient with emphysema the primary aims of treatment are to keep the patient active, to preserve as much lung tissue as possible, and to maintain comfort. The main threat to the patient is further destruction of lung tissue by infection. Therefore, all respiratory infections should be treated vigorously for an adequate period of time. In each patient, efforts should be made to find the cause of the infection. Sputum and blood should be cultured. Antibiotic therapy must be directed toward eradicating the organism causing the disturbance. Satisfactory sensitivity tests are extremely important. While awaiting the culture report, we usually use the following plan: If the patient has fever we treat him with procaine penicillin G, 300,000 units given every 12 hours, on the theory that this may be a pneumococcus type of infection which will respond to penicillin. We assure ourselves that the patient is not sensitive to penicillin by asking him about previous reactions. If he is sensitive to penicillin, erythromycin is used as outlined below. If the patient has no fever but is coughing up purulent sputum, we usually start erythromycin therapy with a dosage of 250 to 500 mg. given four times a day. The rationale is that these infections are frequently staphylococcic in origin and may respond to this therapy. Antibiotic therapy should be given for at least 10 to 14 days if once started.

The next objective of treatment is to keep the patient active. Whenever possible we recommend that he continue his work. A job requiring extensive manual labor may be impossible. Attempts should be made to find a less taxing job. The patient should be urged to exert himself to the extent of his ability and told that shortness of breath acts as a warning sign and means the time to rest is at hand. He need not fear dyspnea, for in itself it is not harmful.

The next aim of therapy is to make the patient comfortable. One of the primary problems is to clear the tracheobronchial tree of thick, tenacious, sticky secretions. Benefit can be obtained with saturated solution of potassium iodide, given in a dose of 15 drops in a half glass of water three or four times a day. This drug seems to modify sputum, in an unknown manner, so as to make it easier for the patient to expectorate. It is the best type of cough medicine to give the patient with chronic emphysema. Cough mixtures containing codeine, morphine, or meperidine (Demerol) hydrochloride, which act by suppressing the cough mechanism, should be avoided. Meperidine, especially, dries secretions and increases the difficulty of clearing the tracheobronchial tree. Bronchodilators are of only limited value in the treatment of emphysema. The patient with emphysema has expiratory airway obstruction, but it is not usually caused by intraluminal obstruction or bronchiolar spasm but by a check-valve mechanism. Because of loss of elastic tissue, the airways are poorly supported. On forced expiration they collapse. When infection occurs, mucosal edema, congestion of blood vessels in the mucosa, and secretions within the lumen of the bronchioles obstruct the airway. Epinephrine and ephedrine constrict mucosal blood vessels and improve air flow. If bronchodilators are given, they should be given both locally and systemically. When the patient inspires, air flows to the areas in the lung with the best ventilation. Therefore, medicine given by aerosol enters the best ventilated parts of the lung and does not penetrate the poorly ventilated parts of the lung where it is needed the most. We have found that some patients benefit from epinephrine, in a 1:1,000 solution, given subcutaneously in doses of 0.3 cc. Isoproterenol, aerosolized as a liquid or powder, is sometimes helpful when spasm contributes to bronchiolar obstruction. The patient may take two or three breaths of this three or four times as needed during the day. This rarely gives relief from dyspnea because of the minor part spasm plays in the ventilatory defect of emphysema, but it has the advantage of being readily available to the patient and affording quick subjective relief.

Types of Treatment

Sedatives.—If the patient can be made to breathe comfortably, he does not need sedatives. Treatment should relieve the cause of dyspnea rather than sedate the patient in an effort to have him sleep in spite of troubled breathing. Heavy sedation is hazardous, because sedatives depress the respiratory center and the patient with emphysema, even though he has dyspnea, is hypoventilating. Avoid the use of morphine and codeine. If sedatives are needed, phenobarbital in a dose of 30 to 60 mg. or chloral hydrate in a dose of 1 to 3 Gm. will give mild sedation without respiratory center depression.

Oxygen Therapy.—Oxygen therapy should be used in the patient with emphysema who is acutely ill with a respiratory infection if hypoxemia is a significant problem. Here it is useful in tiding the patient through a critical period. When the infection is over the patient no longer needs the extra oxygen. It is useful in the late stages of the disease to make the patient more comfortable. We try to avoid long-term oxygen therapy until late in the disease. Some patients become addicted to it and have trouble getting along without it. Dangers accompany the use of oxygen therapy. Since the patient with far-advanced emphysema has pulmonary insufficiency for oxygenation and carbon dioxide elimination, his main stimulus to ventilation is from the chemoreceptors in the carotid and aortic bodies. These receptors are sensitive to a low partial pressure of oxygen in the arterial blood. When oxygen in the arterial blood is increased, the chemoreceptors no longer send messages calling for increased ventilation. Since the respiratory center in the brain is insensitive to carbon dioxide, hypoventilation may follow with further accumulation of carbon dioxide and eventual carbon dioxide narcosis. It is our policy to give patients oxygen therapy intermittently for 20 or 30 minutes each hour.

Breathing Exercises.—A number of physicians who treat patients with pulmonary emphysema have been enthusiastic about the benefits of breathing exercises. The patient needs to have a clear understanding of the pathophysiology of his disease. He may have already learned to breathe out slowly and with pursed lips. If he has been told that this type of breathing actually helps to hold his airways open during expiration, it reinforces what he has found out for himself. The success of breathing exercises depends on the enthusiasm of the physician and the attractiveness of the physiotherapist. In our experience the patients use these exercises faithfully for a while, but as time goes along they tend to abandon them.

Intermittent Positive-Pressure Breathing.—For a while it was hoped that a new gadget, the Bennett valve, was going to be the answer to the problem of emphysema. The initial enthusiasm for this device has now worn off. Although it is helpful in some cases, it is not helpful in the majority. The principle of the machine is as follows: As soon as the patient starts to breathe in, a valve opens and provides air or oxygen at a constant flow. When inspiration stops, the pressure goes on being applied until it reaches a preset point at which the valve turns off and an exhaust opens. Thus, at the end of the patient's normal breath, additional gas is forced into the lung which distends the lung. The patient with emphysema has little trouble getting air in. His main problem is blowing his air out. A disadvantage of the apparatus is that it gives no help in expiration, where the help is desperately needed. A hazard of the apparatus is that the gas goes to the best ventilated parts of the lung. If the alveolar walls in these areas are thin, there is a chance of rupture of the alveoli or even rupture of the lung, especially if the machine has been set to appreciably overdistend the lung. Fowler and coworkers [2] and Leslie and associates [3] have studied intermittent positive-pressure breathing in patients with emphysema. They found that it was an elegant way to administer bronchodilator drugs but that there was little or no benefit from the positive pressure itself.

Steroid Therapy.—Steroids are of little value in the treatment of primary emphysema. Enthusiastic reports regarding steroid therapy in patients with emphysema are the result of their use in patients with bronchial asthma and secondary emphysema. Patients with bronchial asthma respond well to steroid therapy. This reemphasizes an earlier point: it is extremely important to discover the cause of the patient's emphysema. If emphysema is secondary to another type of lung disease, the primary treatment should be aimed at the underlying lung disease.

Pneumoperitoneum.—The administration of air into the peritoneal cavity to raise the diaphragm and improve the expansion of the lung has been advocated for a number of years. The theory is that in emphysema the diaphragm becomes flat at the end of expiration instead of concave or saucer shaped. Air under the diaphragm tends to restore the normal shape to the diaphragm by providing positive pressure from below. The lungs, however, may compensate for this increased pressure from below by increasing the anteroposterior diameter at the end expiratory position so that when the patient is ready for the next breath his vital capacity is unchanged, although a greater proportion of the vital capacity comes from movement of the diaphragm than it did previously. This therapy is still used some, but there is little objective evidence to support it.

Artificial Ventilation with a Respirator.—The respirator does have a definite place in the treatment of patients with respiratory acidosis. In this situation the main problem is hypoventilation. If the pa-

tient can receive adequate ventilation to oxygenate the blood and eliminate carbon dioxide from the blood, he will be improved. We find it most useful in patients who have severe emphysema and an acute infection. One disadvantage is that many patients have great difficulty in adjusting their normal ventilation to that of the respirator. Such conflict may make the patient worse instead of better. Under these circumstances, intermittent positive-pressure breathing which is initiated by the patient's inspiratory efforts may be helpful. Another disadvantage is that adequate respirator care requires trained physicians, nurses, and attendants. This arrangement usually can be found only in a large hospital center.

Smoking.—Lowell and co-workers [4] have presented statistical evidence which suggests that smoking is a cause of pulmonary emphysema. We have seen severe emphysema in a few patients who have been nonsmokers. Although this suggestion is held valid by some, it is not established. In our patients with emphysema, we recommend that they stop smoking if possible. We do not demand that they do so. Some patients are happier if they can still smoke a few cigarettes a day, and we have been willing to make this compromise.

Surgery.—Surgical removal of part of the lung in emphysema has been recommended. The theory is that if a portion of the lung is cystic and overdistended it compresses and prevents proper function of adjacent normal lung tissue. This has been demonstrated in patients with localized cysts of the lung. In the generalized form of the disease, however, removal of one section of the lung results in overdistention of another section and is of no benefit to the patient. In our experience this has not been a helpful procedure, and we do not recommend surgical removal of parts of the lung in the patient who has generalized emphysema.

Summary and Conclusions

It is important to differentiate primary emphysema from emphysema secondary to other types of lung disease. When emphysema is secondary to asthma or other lung disease, therapy should be directed to the primary disease. When emphysema exists as a primary disorder, the aims of therapy are to preserve lung tissue, keep the patient active, and make him comfortable.

Preservation of lung tissue is done by treating all respiratory infections vigorously. The patient with emphysema should be urged to continue work whenever possible. He may exert himself to the point of dyspnea. He can be made more comfortable by means of medication; however, care must be exercised in the selection of the proper drugs so that secretions are not dried out and the respiratory center is not depressed. There is no magic device which is the answer to the problem of pulmonary emphysema. The responsibility of the physician is to give the patient a clear understanding of his disorder and to counsel him concerning how his life can be regulated within the limitations imposed by this disease. In emphysema, as in other diseases, the patient needs a physician and not a gadget.

References

1. Bates, D. V.: Impairment of Respiratory Function in Bronchial Asthma, Clin. Sc. **11:**203-207 (May) 1952.

2. Fowler, W. S.; Hemholz, H. F., Jr.; and Miller, R. D.: Treatment of Pulmonary Emphysema with Aerosolized Bronchodilator Drugs and Intermittent Positive Pressure Breathing, Proc. Staff Meet. Mayo Clin. **28:**743-751 (Dec. 30) 1953.

3. Leslie, A.; Dantes, D. A.; and Rosove, L.: Intermittent Positive Pressure Breathing: Appraisal of Use in Bronchodilator Therapy of Pulmonary Emphysema, J. A. M. A. **160:**1125-1129 (March) 1956.

4. Lowell, F. C.; Franklin, W.; Michelson, A. L.; and Schiller, I. W.: Chronic Obstructive Pulmonary Emphysema: Disease of Smokers, Ann. Int. Med. **45:**268-274 (Aug.) 1956.

AGE AND TASTE SENSITIVITY.—A sipping technique was used to test 100 subjects, aged 15 to 89, for taste sensitivity to substances of a sweet, sour, salty, and bitter nature. It was found that the curve of development and decline for sensitivity to each of the 4 taste primaries was essentially the same. All curves showed a noticeable decline after the late fifties. No sex differences were observed nor were there any differences in taste sensitivity between smokers and nonsmokers. . . . The decreasing sensitivity to taste with age is probably due to certain degenerative changes occurring in the taste receptors. . . . Anatomical studies indicate that such changes do occur. Allara reports that the gustatory papillae reach full development at puberty and that regressive changes set in after the age of 45. Furthermore, both Machizuki, studying the foliate papillae, and Arey, Tremain, and Monzingo the circumvallate papillae, report a decrease in number of papillae with age. In addition to a decrease in number of papillae there is also a decrease in number of taste buds. Arey and associates report that in young adults there are approximately 250 taste buds in each circumvallate papilla; over the age of 70 there are less than 100.—R. M. Cooper, I. Bilash, and J. P. Zubek, *Journal of Gerontology*, January, 1959.

RADIOACTIVE ZINC IN THE PROSTATE

SOME FACTORS INFLUENCING CONCENTRATIONS IN DOGS AND MEN

George R. Prout Jr., M.D., Michael Sierp, M.D.
and
Willet F. Whitmore Jr., M.D., New York

The concentration of zinc in the prostate gland was studied in dogs with prostatic fistulas by injecting the radioactive isotope Zn^{65} intravenously. The ability of the canine prostate to concentrate and secrete zinc was demonstrated. The amount of zinc stored in the gland decreased after orchiectomy and increased greatly after administration of testosterone. It was also found possible to study the concentration of zinc in the human prostate by the preoperative intravenous injection of 108 to 150 μc of Zn^{65} and the subsequent examination of normal and abnormal prostatic tissue removed in such operations as radical cystectomy. The normal prostate contained more Zn^{65} than did any other normal tissues examined, and neoplastic prostatic tissue generally contained less than normal prostatic tissue or tissue manifesting benign hyperplasia.

The first measurement of zinc in the prostate by Bertrand and Vladesco [1] in 1921 resulted in subsequent experiments designed to clarify the role of this trace metal in the mammalian prostate. Mawson and Fischer [2] have shown that the prostate contains a higher concentration of zinc than do any of the other soft tissues they measured in the human. They demonstrated that concentrations of zinc in normal prostatic tissue and benign hypertrophy are about equal but that prostatic carcinoma and prostatic infection are associated with decreased concentrations of zinc. Hoare, Delory, and Penner [3] found low zinc values in benign hypertrophy and prostatitis and even lower concentrations in carcinoma. Gunn and Gould [4] have demonstrated a difference in the concentration of radioactive zinc between the lateral and dorsal prostate of the rat, also that localization of concentrations of zinc occur in these structures under various endocrine influences.

With the use of dogs prepared with prostatic fistulas, we have previously demonstrated that the intravenously injected radioactive isotope of zinc, Zn^{65}, will appear in a highly predictable manner after stimulation with pilocarpine sulfate for at least 150 days and that concentration of radioactivity was nearly always greater in the first portion of dog prostatic fluid collected.[5] Biopsy of several organs in an intact dog seven days after the injection of 100 μc of Zn^{65} revealed far more radioactivity in the prostate than in any other organ sampled. Estradiol produced a rapid drop in volume and in both concentration and total amount of radioactivity in dog prostatic fluid.[5] Daniel and co-workers [6] demonstrated that intravenously administered Zn^{65} is concentrated in the human prostate and, by radioautographic techniques, they localized the Zn^{65} to the prostatic epithelium.

Methods and Material

Prostatic fistulas were created by the technique of Huggins.[7] After recovery, prostatic stimulation was accomplished by giving 5 mg. of pilocarpine sulfate (1 mg. per milliliter) intravenously at time zero. Dog prostatic fluid (DPF) was collected in two time-determined aliquots, the volume estimated, and the fluid volumetrically transferred to 5-ml. counting vials. DPF 1 was collected from time zero to 15 minutes and DPF 2 from 15 to 30 minutes after administration of pilocarpine.

The radioactive isotope of zinc, Zn^{65}, was obtained as zinc chloride with a carrier content of less than 300 mcg. per millicurie. The isotope was administered intravenously in every instance. Radioactivity was determined in a well-type scintillation counter, usually counting 1 or 2 ml. of prostatic fluid. The radioactivity recovered in 1 ml. of prostatic fluid is expressed as a percentage of the total radioactivity administered. This value is expressed as 10^{-3} in the data and is henceforth referred to as radioactivity in dog prostatic fluid.

Tissues obtained by biopsy were placed in preweighed vials and were weighed again immediately. Each vial was then frozen until radioactivity was determined. The percentage of the injected dose in each sample was expressed as radioactivity per gram of wet tissue (10^{-3}). Acetazolamide (Diamox) was injected intravenously immediately before pilocarpine was given or as indicated. The chemical analysis of sodium, potassium, chloride, and the carbon dioxide combining power were carried out according to suitable laboratory methods as re-

From the Urologic Service, Department of Surgery, and the Division of Experimental Surgery of the Sloan-Kettering Institute, Memorial Center for Cancer and Allied Diseases. Dr. Prout is now at the University of Miami School of Medicine, Miami, Fla.

Read before the Joint Meeting of the Section on Pathology and Physiology and the Section on Urology at the 107th Annual Meeting of the American Medical Association, San Francisco, June 26, 1958.

ported elsewhere.[8] The hydrogen ion concentration of the prostatic fluid was estimated at 1 minute and 17 minutes after the injection of pilocarpine, with the use of pHydrion indicator paper. Crystalline preparations of testosterone and estradiol were given intramuscularly as indicated in the animal experiments. Ethinyl estradiol or chlorotrianisene (Tace) was given to men as indicated.

TABLE 1.—*Radioactivity in Canine Prostate*

	Intact			Testosterone 10 Mg./Day	Estradiol 12.5 Mcg./Day	Orchiectomy Performed Day Zero
Dog	X227	X22	X4	X371	X344	X262
Zn^{65} μc	255	250	100	146	146	195
Days after injection						
5	39	22	...	249	169	16
7	...	...	300	...	...	...
14	133	152	...	731	105	4

Experiments on Dogs

EXPERIMENT 1.—Six dogs were involved in this experiment. Dogs X22 and X227 were given, respectively, 250 and 255 μc of Zn^{65}, and biopsies were performed on the prostates at 5 and 14 days thereafter. There were higher concentrations of radioactivity in the second biopsy specimens. Dog X4 was given 100 μc of Zn^{65}, and a biopsy was performed on the prostate on the seventh day. The concentration of radioactivity was greater than in any of the specimens taken from the other dogs, except the one influenced by testosterone.

Dog X371 was given 146 μc of Zn^{65} on day zero and also started on therapy with testosterone, 10 mg. intramuscularly daily. Biopsy specimen on the fifth day showed

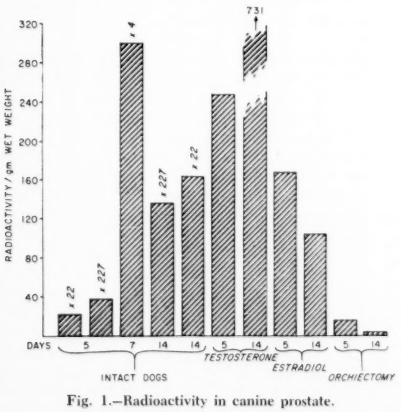


Fig. 1.—Radioactivity in canine prostate.

far greater concentration of radioactivity than did the controls (dogs X22 and X227). At 14 days, exogenous testosterone administration was associated with a continued pronounced rise in concentration of radioactivity to about five times the values in the control studies.

Dog X344 was given 146 μc of Zn^{65} on day zero and was also started on therapy with estradiol, 12.5 mcg. intramuscularly daily. Dog X262 was given 195 μc of Zn^{65} on day zero and was castrated on the same day. These dogs were also subjected to prostatic biopsy on the 5th and 14th days. Results are shown in table 1 and figure 1.

EXPERIMENT 2.—After a prostatic fistula had been constructed and a control period of 21 days completed, dog X55 received testosterone, 10 mg. daily intramuscularly. Fourteen days later bilateral orchiectomy was carried out and five days after that the dog was injected with 129 μc of Zn^{65}. Prostatic fluid was obtained at varying intervals thereafter. The results are shown in table 2 and figure 2.

Prior to the institution of exogenous testosterone, the volume of DPF produced and the concentration of radioactivity were both low in dog X55. When testosterone was given daily and the dog subsequently castrated, the volumes of DPF 1 and 2 were maintained at average levels of nearly 20 ml. and 8 ml. respectively. Radioactivity in DPF 1 and 2 reached peaks of 56 and 32 on the 7th day, and 14 and 6 on the 38th day after injection of 129 μc of Zn^{65}.

TABLE 2.—*Radioactivity and Volume of Dog Prostatic Fluid in Dog X55 Given 106 μc of Zn^{65} on Day Zero*

	Radioactivity			Volume, Ml.	
Days	DPF1†	DPF2†		DPF1†	DPF2†
1	15	...‡		3.5	...‡
4	13.5	4.0		4.0	1.5
7	5.0	5.0		3.0	3.0
10	13.0	8.0		8.0	3.5
14	7.5	1.5		8.0	4.0
18	5.0	2.0		4.0	...‡
21	2.0	1.5	← Testosterone 10 mg. daily commenced →	8.0	4.0
24	2.5	2.0		13.0	5.0
28	2.1	1.0		16.0	6.0
31	1.5	1.0		18.0	7.0
35	1.5	1.0	← Bilateral orchiectomy →	18.0	5.0
39	2.0	1.0		13.0	5.0
			← Zn^{65} 129 μc day 40 →		
42	2.0	1.0		20.0	5.0
49	56.0	32.0		20.0	5.0
52	41.5	20.5		25.0	9.0
56	38.0	21.0		20.0	5.0
59	29.0	11.0		24.0	6.0
64	21.0	10.0		21.0	11.0
69	19.0	9.0		19.0	9.0
71	10.0	9.0		15.0	5.0
75	13.0	6.5		17.5	9.0
78	14.0	6.0		20.0	5.0

†DPF1 = fluid collected 0 to 15 minutes; and DPF2 = from 15 to 30 minutes after injection of pilocarpine.
‡ DPF1 and DPF2 combined.

EXPERIMENT 3.—Dog X75, after complete recovery from the creation of a prostatic fistula, was given 66 μc of Zn^{65}. DPF was collected at varying intervals thereafter. Details of this experiment are published elsewhere.[5] The results are shown in table 3 and figure 3.

EXPERIMENT 4.—Control studies on the ionic constituents of DPF 1 and 2 were obtained. Acetazolamide was given intravenously at time zero in amounts varying between 95 and 128 mg. per kilogram to several different dogs in which prostatic fistulas had been created. The results of this experiment are shown in table 4.

Control studies on the ionic constituents of prostatic fluid need little comment. The potassium level was always less in DPF 2 than in DPF 1, the aver-

age values being 6.6 mEq. and 3.9 mEq. per liter. Sodium was nearly always less in DPF 1 than in DPF 2, the average values being 149 mEq. and 152 mEq. per liter. The same was true of the chloride, the average values being 161 mEq. per liter for DPF 1 and 162 mEq. per liter for DPF 2. Bicarbonate ion was so low as to constitute a qualitative rather than a quantitative assay. When acetazolamide was given intravenously, no remarkable departure from the control studies could be detected.

EXPERIMENT 5.—After complete recovery from the creation of prostatic fistulas and after orchiectomy and the institution of testosterone therapy, 10 mg. intramuscularly daily, dogs X656 (weight 26 kg.) and X266 (weight 16 kg.) were given 272 μc of Zn^{65} each on day zero. Acetazolamide in 100 mg. per kilogram dose was given intravenously thrice to the former and four times to the latter. Volume and radioactivity in DPF 1 and 2 were recorded. The results are shown in table 5 and figure 4.

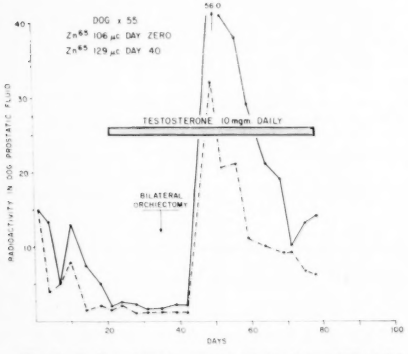


Fig. 2.—Radioactivity in prostatic fluid of dog X55. Solid line indicates fluid collected from 0 to 15 minutes; dotted line, from 15 to 30 minutes after injection of pilocarpine.

When acetazolamide was given to dogs who had received Zn^{65}, a peak of 71.4 in DPF 1 was seen in dog X266, but subsequent concentrations of this magnitude were not observed in this animal nor in dog X656, whose highest value of radioactivity was 21.7. No remarkable alteration in the concentration of radioactivity occurred in DPF 2 in either animal nor in the volume produced.

Estimation of the hydrogen ion concentration in experiments 4 and 5 was done more than 50 times. The pH controls revealed a usual decrease in pH from 5.5 to 5 between DPF 1 and 2. Occasionally the pH was as high as 6 or as low as 5 in DPF 2, and occasionally the decrease in pH in DPF 2 failed to occur. Administration of acetazolamide failed to alter these patterns in any way.

Report of Cases

Men with various urologic disorders were given between 108 and 150 μc of Zn^{65} intravenously, and tissue was subsequently obtained at operation by sharp dissection and never washed or immersed in fluid. The posterior lamella of the prostate was separately assayed when it could be distinctly identified. The prostatic tissue designated as "normal" was obtained immediately after radical cystectomy in each instance. Cowper's gland was removed in each instance during perineal dissection. Each anatomic and pathological diagnosis was substantiated histologically. Minor inflammatory responses were ignored in the pathological diagnosis. Only the major histological feature of each gland was recorded. Radioactivity in the blood is not

TABLE 3.—*Radioactivity and Volume of Dog Prostatic Fluid in Dog X75 Given 66 μc of Zn^{65} on Day Zero*

Days After Injection	Radioactivity		Volume, Ml.	
	DPF1[1]	DPF2[1]	DPF1[1]	DPF2[1]
1	29.9	17.1	6.0	5.0
3	25.9	17.6	8.0	4.5
6	34.0	19.9	10.0	5.0
8	20.0	15.4	8.0	4.0
11	24.3	11.5	9.0	5.0

[1] DPF1 = fluid collected 0 to 15 minutes; DPF2 = from 15 to 30 minutes after injection of pilocarpine.

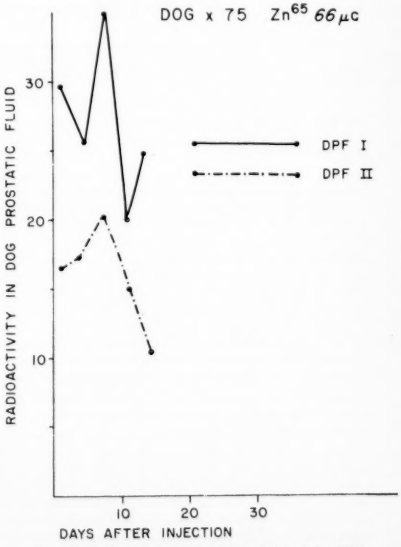


Fig. 3.—Radioactivity in prostatic fluid of dog X75.

shown because many of the patients received transfusions in varying amounts during the surgical procedures.

Case 6.—A 60-year-old man had undergone an abdominal-perineal resection for adenocarcinoma of the rectum 20 years prior to admission for progressing signs of bladder neck obstruction. A transurethral resection was carried out and adenocarcinoma was diagnosed histologically. Two days after the administration of Zn^{65}, a radical cystectomy was carried out. The prostate was small and seemed fibrotic. A biopsy was taken of the more centrally placed portion of the prostate for the determination of radioactivity. Aside from scant inflammatory response, adenocarcinoma was again noted.

Case 7.—A healthy, sexually active, asymptomatic, 62-year-old man was told during a routine physical examination that he had a nodule in his prostate. The nodular area was confined to the capsule of the right lobe and measured about 10 mm. in greatest diameter. Two and a half days after the injection of Zn^{65}, perineal exploration and biopsy of this nodule and the opposite prostatic lobe were performed and specimens submitted for histological examination and radioactivity assay. Carcinoma was present in the nodule only.

Case 9.—An 81-year-old male had undergone three transurethral resections for an infiltrating carcinoma of the bladder and had also had partial transurethral resection of the prostate prior to radical cystectomy. He was in good health aside from cardiovascular disease. The prostate was enlarged with a firm nodule on its posterior surface that was suggestive of primary carcinoma. Zn^{65} was given a day and a half before operation. A portion of the posterior lamella of the prostate stripped readily from the radical cystectomy specimen, was separately excised, and the radioactivity determined. A deeper section of the prostate was also excised and the radioactivity determined. Histological sections of the prostate revealed adenocarcinoma in addition to some inflammatory response.

Case 12.—A 70-year-old man had been treated by transurethral resection for sarcoma of the prostate. The sarcoma could be felt at the base of the right lobe extending into the region of the right seminal vesicle. Four days after the injection of Zn^{65}, a radical cystectomy was performed and sections from the tumor, the uninvolved posterior lamella, and the more centrally placed prostatic tissue were examined for radioactivity.

Case 17.—A 70-year-old man had minimal urinary symptoms and was in good general condition. A firm, 12-mm., nodular mass was palpable at the base of the prostate. After exposure perineally, this mass was thought to be an area of adenomatous hyperplasia with infection present. This impression was corroborated histologically. The radioactivity present in the capsule and hyperplastic prostate was determined.

Concentrations of Radioactivity in Human Tissues

In each of the three patients whose prostates were considered normal, the concentration of radioactivity was higher in the prostate than in any of the other tissues on which biopsy was performed. The values for prostatic radioactivity in these three patients ranged from 14.0 to 5.3. In the one patient in whom the radioactivity of Cowper's gland was determined, the concentration was 3.8 (table 6).

Two of the patients suffering from carcinoma of the prostate were in relapse. Orchiectomy had been done two years previously in case 15 and six months earlier in case 13. These two patients had concentrations of 4.4 and 5.6, respectively, in their prostatic tissue. Lymph nodes removed from one during celiotomy were found to have tumor tissue present, with activities of 5.7, 6.3, and 7.8 (table 7).

One man (case 14) was given chlorotrianisene for six months without benefit of histological diagnosis of cancer. The clinical diagnosis of cancer was confirmed by biopsy of his prostate six weeks after the last dose of chlorotrianisene and three days after Zn^{65} had been given. In this patient and in eight other untreated patients with carcinoma of the prostate, the radioactivity in the prostate ranged from 12.7 to 1.8, the average being 5.5. Radioactivity in the isolated case of sarcoma of the prostate was 5.6 (table 7, case 12).

In one patient (case 7) the sharply demarcated malignant area in the prostate had a concentration of 5.1, while the adjacent tissue had a concentration of 9.6. In another man (case 9) the posterior lamella, presumed free of disease, was 6.8. This sample of tissue as well as corresponding samples obtained from the prostates of two other patients (cases 12 and 13) were not examined histologically, but no doubt exists as to the over-all diagnosis in the individual prostates (table 7).

In the other genital appendages and testes on which biopsy was performed, concentration of radioactivity was always less than in the prostate, except in one man (case 5) whose epididymis had a radioactivity of 7.1 as opposed to 6.8 for prostatic radioactivity and in another man (case 10) whose testis had only slightly greater activity than the

Table 4.—*Control Determinations and Effect of Intravenously Administered Acetazolamide on Ionic Constituents of Dog Prostatic Fluid*

Control*	Sodium, mEq./Liter	Potassium, mEq./Liter	Chlorine, mEq./Liter	Bicarbonate Radical, mM./Liter†
DPF1‡	149	6.6	161	1.8
DPF2	152	3.9	162	1.3
After Acetazolamide				
DPF1	147, 145, 147, 149	5.8, 6.2, 6.5, 5.8	160, 161, 163, 170	1.8, 2.4, 5.4, 1.3
DPF2	158, 153, 146	4.3, 4.3, 2.6, 3.8	165, 163, 163, 163	2.0, 2.0, 1.8, 1.7

* Fluid collected under oil.
† These figures represent an average of not less than 10 determinations in each category.
‡ DPF1 = fluid collected from 0 to 15 minutes; DPF2 = from 15 to 30 minutes after injection of pilocarpine.

prostate. Epididymal concentrations of radioactivity ranged from 0.9 to 7.1, and testicular concentrations from 1.6 to 3.3. Radioactivity in the vas varied from levels too low to be significant to 4.2 (table 7).

Of the nine patients with benign prostatic hyperplasia, the adenomas contained concentrations of radioactivity varying from 22.1 to 3.2, while the capsular concentration varied from 8.6 to 2.1 (table 8). Three men (cases 21, 22, and 23) received estrogen therapy in association with the administration of isotope and before prostatectomy. In these three the adenomas had radioactivity varying between 7.7 and 7.0. In two the capsular concentrations of radioactivity were 8.4 and 3.6, and in one of these was seen the greatest concentration of radioactivity in the vas (6.6). Another patient received exogenous testosterone therapy and had a concentration of radioactivity of 10.6 in the adenoma and 2.1 in the capsule. The concentrations of radioactivity in the seminal vesicle of intact men not receiving hormone treatment varied from 0.7 to 4.6. In the one patient in this group in whom the radioactivity of Cowper's gland was determined, the concentration was 2.2 (table 8).

Dog Prostatic Fluid

Since it has been demonstrated that after the intravenous administration of radioactive zinc, Zn^{65}, the concentration of that isotope in dog prostatic fluid is related to time as well as to health and general condition,[9] it seems reasonable to expect a reflection of this phenomenon in the concentration of radioactive zinc in the prostate. As demonstrated, such is the case (experiment 1, table 1, fig. 1). It is probable that we have missed the actual peaks of concentrations, especially in the prostatic tissue, but from data concerning radioactivity in DPF 1

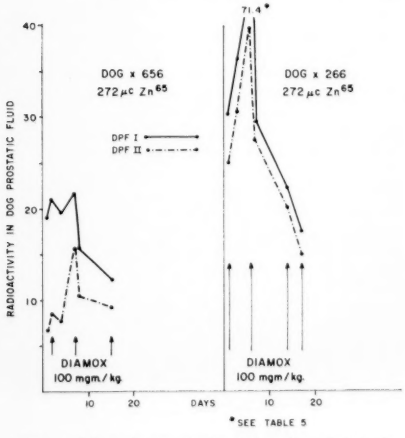


Fig. 4.—Effect of acetazolamide (Diamox) on Zn^{65} in dog prostatic fluid.

TABLE 5.—*Effect of Acetazolamide on Volume and Concentration of Zn^{65} in Dog Prostatic Fluid*

Days After Injection of Zn^{65}	Radioactivity DPF1†	Radioactivity DPF2†	Volume, Ml. DPF1†	Volume, Ml. DPF2†	Acetazolamide, Gm.
Dog x 656 Zn^{65} 272 μc					
1	19.2	6.8	20.0	9.0	
2	21.0	8.5	19.0	8.0	2.6‡
4	19.6	7.8	27.0	8.0	
7	21.7	15.7	18.0	5.5	2.5
8	15.8	10.4	24.0	6.5	
15	12.3	9.2	33.0	6.5	2.5
Dog x 266 Zn^{65} 272 μc					
1	30.4	25.0	36.0	8.5	1.6
3	36.5	30.7	32.0	2.5	
6	71.4§	40.0	8.0	8.0	1.6
7	29.4	27.6	30.0	9.5	
14	22.3	20.3	32.0	11.0	1.5
17	17.5	15.0	37.0	9.0	1.5

† DPF1 = fluid collected 0 to 15 minutes; DPF2 = from 15 to 30 minutes after injection of pilocarpine.
‡ Given at 15 minutes; rest given at 0 minutes.
§ First portion lost.

and DPF 2 [5] as well as from information regarding prostatic biopsies,[9] it seems reasonable to conclude that although each animal concentrates Zn^{65} in an individual manner, most dogs probably reach a peak of concentration within two weeks. It seems unlikely that the peak of concentration of radioactivity in prostatic fluid occurs much before five days.

Huggins and associates [10] observed that caged dogs responded to their environment by becoming azoospermic. Weight loss, shedding, and loss of appetite are other manifestations of an adverse response to caging. It is impossible to ascertain the amount of prostatic fluid such dogs might produce under natural conditions. Most impressive is the response in terms of exaggerated production of DPF to exogenous testosterone when compared to the control period in the same dog or to other dogs dependent on endogenous androgen alone. There is also a remarkable increase in the concentration and total amount of radioactive zinc produced during the period of testosterone administration as compared with the control period in the same animal (experiment 2, table 2, fig. 2). It is conceivable that the lesser volumes and radioactivity we usually collect are the result of decreased gonadotropin production, while the response to exogenous testosterone represents more nearly the normal physiological state. Leaving these considerations aside, it is clear that the presence of radioactive zinc in the prostate and dog prostatic fluid is an androgen-dependent phenomenon, be it endogenous or exogenous in origin.

It is of interest that the total amount of Zn^{65} produced in one hour reaches relatively high levels, particularly during the first two weeks after the

injection of the isotope. Dog X75 has been demonstrated to produce volumes and concentrations of radioactivity in DPF 3 (prostatic fluid secreted between 30 and 60 minutes) that are usually equal or slightly lower than those found in DPF 2.[5] Since Huggins and associates [10] have shown that 95% of the volume of prostatic fluid is produced in one hour after pilocarpine injection, the amount of radioactivity produced by X75 on any of the days shown can be calculated from table 3, assuming that total radioactivity found in DPF 3 is 90% of that found in DPF 2. Though some objection may be raised, this maneuver seems reasonable in view of this animal's previous performance.[5] Hence, on the sixth day after the injection of the isotope, about 0.54% of that dose was secreted. On the 8th and 12th days 0.28 and 0.33%, respectively, of the injected isotope was produced (experiment 3, table 3, fig. 3). Unless some hormonal influence, illness, or other catastrophe should occur, the production of DPF and radioactive zinc in similar but ever decreasing amounts will continue. This dog weighed about 18 kg., and his prostate can scarcely have exceeded 10 Gm. in weight.[11] Bearing in mind the

TABLE 6.—*Radioactivity in "Normal" Prostate in Carcinoma of the Bladder**

Case	Age	Sexual Intercourse	Day After Zn^{65} Injection	Prostate	Cowper's Gland	Seminal Vesicle	Vas	Epididymis	Testis	Striated Muscle
1	63	?	5	9.6	3.8	3.3	3.9	5.9	2.8	...
2	69	?	2	14.0	...	1.0	...	...	1.6	3.8
3	54	Once a wk.	4	5.3	...	4.0	...	...	...	1.0

*All patients were in good general condition.

observations that the prostates of the intact control animals have maximal concentrations of radioactivity per gram of 0.039% on the 5th day and 0.152% on the 14th day (table 1, fig. 1), it seems that the prostate must be continuously replenishing itself with the isotope rather than storing a maximal concentration during the short initial period of relatively high blood and plasma concentrations. This is buttressed by the observation that X75 and all the other dogs we have studied continued to produce relatively large amounts of isotope in addition to the fact that the control animals were never subjected to the depleting effects of pilocarpine.

We are unable to explain the alterations in the concentrations of isotope in dog prostatic fluid [5] (fig. 2, 3, and 4) and in the prostate over the first two-week period of observation. It is conceivable that Zn^{65} is being incorporated into a protein complex and that this is a time-consuming process evidenced by the lag in maximal concentration in both gland and fluid. If such were the case, one would not expect the prostate to be able to produce the relatively large amounts of isotope that it does on repeated stimulation in view of the known prostatic concentration.

Orchiectomy produces a prompt, impressive decrease in the concentration of Zn^{65} in the dog prostate. Fourteen days after orchiectomy, the concentration of radioactive zinc in the canine prostate is only 3% of the lower control value (dog X22, table 1). When estradiol was given, the volume and the concentration and total amount of Zn^{65} produced were decreased.[5] The decrease in the volume of prostatic fluid produced is more readily assessed than the alteration in Zn^{65} secretion but prostatic biopsies reveal a distinct decrease in Zn^{65} concentration. The 14-day value for radioactive zinc concentration during the administration of estradiol is 78% of the lower control value and 69% of the higher (table 1). These values are appreciably higher than those obtained after orchiectomy but it is conceivable that, had we waited for a longer period of time, the radioactivity would have dropped to lower levels. It is clear that orchiectomy acts more promptly and possibly more effectively in decreasing the concentration of Zn^{65} in the prostate than does estradiol.

Since zinc is the prosthetic metal associated with carbonic anhydrase, it seemed reasonable to attempt evaluation of the role of carbonic anhydrase in producing dog prostatic fluid. Huggins [7] has described the ionic constituents of dog prostatic fluid, but to record any acute alterations controls must first be established. Even though Mawson and Fischer [12] have demonstrated that in the prostates of the rat and rabbit there is far more zinc than can be accounted for by the presence of carbonic anhydrase, we felt it worthwhile to measure the concentration of Zn^{65} in the prostatic fluid of dogs after the intravenous injection of relatively large doses of acetazolamide, a substance demonstrated to effectively inhibit carbonic anhydrase activity.[13] We also measured volume and ionic concentrations and crudely estimated the hydrogen ion concentration. Any alteration that occurred in these features seemed to fall within the range of our established norms. The bicarbonate ion may be significantly elevated, but these levels leave doubt as to technical accuracy. It seems reasonable to conclude that acetazolamide does not effectively alter the volume, pH, ionic constituents, or Zn^{65} concentration in either DPF 1 or DPF 2. We do not necessarily conclude that carbonic anhydrase plays no role in the production or constitution of dog prostatic fluid (experiments 4 and 5, tables 4 and 5, fig. 4).

Prostatic Concentrations in Men

Acetazolamide was given in doses as high as 1 Gm. daily to six men with prostatic adenocarcinoma. No objective or subjective alteration in the patients' courses could be ascertained, even in terms of hours. When Zn^{65} was injected intravenously into men with no prostatic disorder, the

prostate contained significantly more isotope than the other tissues on which biopsy was performed. Intact men with carcinoma of the prostate also had a higher concentration of Zn^{65} in their respective neoplastic glands than in nearly all of the other tissues. In general, the trend of the values is lower in the neoplastic gland than in the "normal" prostates or in the adenomas of benign hyperplasia. There are five determinations below 5.0 in the carcinoma group and only one below 5.0 in the "normal" and adenomatous groups. The sum of the patients without neoplasia makes a numerical group suitable for comparison with those intact patients with carcinoma (tables 6, 7, and 8). We were able to demonstrate that one clearly neoplastic area contained less Zn^{65} than adjacent histologically normal prostatic tissue (table 7). It would be erroneous to conclude that neoplastic tissue had less Zn^{65} in it except at the time biopsy was here except for one patient with adenocarcinoma of the prostate. This man's concentration of prostatic radioactivity was 28, a figure over twice our greatest concentration in patients with this disease. Until more information is accumulated, this concentration must be viewed as a departure from the usual trend.

Orchiectomy was not associated with a dramatic decrease in Zn^{65} concentration in the neoplastic gland. For points of reference one may refer to the unaltered concentration of Zn^{65} in striated muscle (table 7). We have to date not done the obvious experiment of taking a biopsy specimen of the prostate before and after orchiectomy. The lymph nodes in which metastatic disease was present all had radioactivity comparable to that of the primary tumor. Retrospection makes obvious the need for radioactivity determinations in uninvolved nodes.

TABLE 7.—*Radioactivity in Neoplastic Prostate*

Case	Age	General Condition	Sexual Intercourse	Days After Zn^{65} Injection	Neoplasm	Adjacent Normal Prostate	Lymph Node Metastases	Seminal Vesicle	Vas	Epididymis	Testis	Striated Muscle
4.....	68	Fair	?	4	2.1	...	...	...	X, X	0.9 0.9	1.7 1.6	...
5.....	53	Excellent	Twice a wk.	2	6.8	...	...	...	...	7.1	...	...
6.....	60	Good	?	2	1.8	...	...	6.7	...	...	...	...
7.....	62	Excellent	Twice a mo.	2.5	5.1	9.6	...	2.8	4.2	4.4	2.4	...
8.....	67	Good	?	3	12.3	...	...	...	...	...	...	0.6
9.....	81†	Good	Once a mo.	1.5	4.8	6.8 Posterior lamella	...	...	...	...	...	0.7
10.....	69	Good	0	7	2.9	...	...	...	...	2.1	3.3	1.2
11.....	65	Fair	0	2	2.5	...	...	...	...	1.6 1.9	2.1 1.9	...
12.....	70‡	Good	?	4	5.6	1.0, 6.9 Posterior lamella	...	...	...	...	...	1.0
13.....	67§	Fair	0	2	5.6	4.5 Posterior lamella	6.3, 5.7, 7.8	...	...	...	...	1.4
14.....	74‖	Good	?	3	12.7	...	...	...	...	...	...	1.1
15.....	59¶	Poor	0	10	4.4	...	...	...	...	...	...	2.1

† Carcinoma of bladder and prostate.
‡ Sarcoma of prostate.
§ Anaplastic carcinoma of prostate. Orchiectomy performed six months before administration of isotope.
‖ Chlorotrianisene therapy discontinued six weeks before biopsy.
¶ Orchiectomy two years, estrogen stopped six months prior to isotope administration.

performed were it not for data published by Mawson and Fischer[14] on untreated patients with carcinoma of the prostate and Hoare and co-workers[3] indicating that total zinc concentrations in the neoplastic gland are unquestionably lower than in the normal gland. Hence, one might reasonably suppose that the malignant gland would have less Zn^{65} at any given time after injection of the isotope than the "normal" gland.

Daniel and co-workers[6] have reported on Zn^{65} prostatic concentration in 12 patients with various diseases. They chose to report organ/blood ratios rather than percentage of injected dose of isotope. Since many of our patients received considerable volumes of blood during exenteration, and for other reasons as well, it was determined inadvisable to show organ/blood Zn^{65} ratios. Expression of the data presented by Daniel and co-workers as percentage of injected isotope reveals no remarkable departure in values from those we have presented

From the data regarding radioactivity in benign hyperplasia, it is suggested that the prostate capsule contains less radioactivity than the adenoma. We took biopsy specimens from these patients at intervals of one and one-half to seven days after Zn^{65} administration and can only state that during these periods more Zn^{65} was concentrated in the adenoma than in the capsule of the individual gland (table 8). When estrogen was given with, before, or after Zn^{65}, no alteration in concentration of the isotope could be detected from the control levels. The only published data on the effect of stilbestrol on zinc concentration in the human prostate are those of Hoare and associates.[3] They were able to demonstrate a slight decrease in total zinc concentration, roughly approximating our determinations utilizing Zn^{65}. Exogenous testosterone was not associated with any clear-cut alteration in isotope concentration in the single experiment reported (table 8).

Comment

It seems inappropriate to attempt direct application of canine data to human data concerning Zn^{65}. Species difference, difference in relative mammalian age, and prostatic size are obvious objections. This may be particularly true when widespread metastases from carcinoma of the prostate are present. It is conceivable that in our present state of ignorance regarding trace element physiology, we have failed to account for the dilution of the isotope that takes place as a result of the disparity in body mass between mammals, and that, in competing for zinc with other organs, the human prostate does not concentrate the isotope as the dog's does. Nevertheless, it would seem that our canine orchiectomy and testosterone responses are so unequivocal that some alteration in Zn^{65} concentration would be demonstrable in man.

TABLE 8.—*Radioactivity in Benign Hyperplasia of the Prostate**

Case	Age	Sexual Intercourse	Days After Zn^{65} Injection	Adenoma	Posterior Lamella	Cowper's Gland	Seminal Vesicle	Vas	Epididymis	Testis	Striated Muscle
16	68†	Twice a mo.	3	5.6	2.2	...	3.5	...	...	...	0.9
17	70‡	0	7	22.1	8.6	...	3.7	...	...	...	2.0
18	71§	Yes Amt. ?	1.5	8.2	7.1	...	4.1	3.3	...	...	0.5
19	65¶	?	2	6.2	2.4	...	4.6	4.0	3.7	2.3	...
20	73	?	6	3.2	3.1	2.2	...	...	...	...	2.5
21	73§	?	9	7.4	...	...	...	...	...	...	1.4
22	66†‖	Yes Amt. ?	5	7.0	8.4	...	4.0	6.6	...	...	0.9
23	67¶	?	15	7.7	3.6	...	...	...	...	...	...
24	62‡‡	Yes Amt. ?	4	10.6	2.1	...	0.6	...	...	...	...

*All patients were in good general condition.
† Carcinoma of bladder, also.
‡ Prostatitis also.
§ Ethinyl estradiol therapy, 0.5 mg. daily, for nine days before biopsy.
¶ Ethinyl estradiol therapy, 0.5 mg. daily, for two weeks before biopsy.
‖ Ethinyl estradiol therapy, 1 mg. daily, for 10 days before biopsy.
‡‡ Testosterone therapy, 25 mg. daily intramuscularly, for one week before biopsy.

The concentrations of Zn^{65} in the human epididymis, vas, and seminal vesicle are relatively low. The feature these values all seem to have in common is that they are not subject to the wide variations that the prostatic values undergo.

We recognize that the data presented here prevent dogmatic conclusions by virtue of statistical inadequacy alone, but the information thus far obtained regarding radioactive zinc in mammalian genitalia would indicate that the propensity displayed by the prostate for Zn^{65} is an androgen-controlled phenomenon that is adversely affected by orchiectomy and the administration of female hormones in the dog. Irregular, unforeseeable concentrations of the isotope have been found in the human prostate, and it would seem that neoplasms and the prostatic capsules of benign glands have lesser concentrations of Zn^{65} than the normal and the adenomatous glands.

Still unanswered is the major question regarding genital zinc. What is its function? As pointed out elsewhere, sperm are richer in zinc than any human tissue studied, yet the testis is relatively poor in this element.[5] From this observation alone, it would seem that zinc is related to spermatic physiology. It is conceivable that the prostate acts as nothing more than a purveyor and receptacle for zinc until ejaculation occurs and at this time zinc is incorporated in the sperm in a perhaps essential capacity. Certainly, under the conditions of the experiments, the unfailing appearance of Zn^{65} in prostatic fluid and the prostate suggests that prostatic fluid without zinc would no longer be prostatic fluid.

Experiments 1 and 2 are results of work by Dr. Michael Sierp and associates[9a] and will be the subject of more detailed reports.

Data on dog X4 (table 1, fig. 1) and data in table 3 and figure 3 are reproduced with permission from Prout and associates.[5]

References

1. Bertrand, G., and Vladesco, R.: Intervention probable du zinc dans les phénomènes de fécondation chez les animaux vertébrates, Comptr. rend. Acad. d. sc. **173:**176, 1921.

2. Mawson, C. A., and Fischer, M. I.: Occurrence of Zinc in Human Prostate Gland, Canad. J. M. Sc. **30:**336-339 (Aug.) 1952.

3. Hoare, R.; Delory, G. E.; and Penner, D. W.: Zinc and Acid Phosphatase in Human Prostate, Cancer **9:**721-726 (July-Aug.) 1956.

4. Gunn, S. A., and Gould, T. C.: Difference Between Dorsal and Lateral Components of Dorsolateral Prostate of Rat in Zn^{65} Uptake, Proc. Soc. Exper. Biol. & Med. **92:** 17-20 (May) 1956; Relative Importance of Androgen and Estrogen in Selective Uptake of Zn^{65} by Dorsolateral Prostate of Rat, Endocrinology **58:**443-452 (April) 1956.

5. Prout, G. R.; Daniel, O.; and Whitmore, W. F., Jr.: Occurrence of Intravenously Injected Radioactive Zinc in Prostate and Prostatic Fluid of Dogs, J. Urol. **78:**471-482 (Oct.) 1957.

6. Daniel, O.; Haddad, F.; Prout, G. R.; and Whitmore, W. F., Jr.: Some Observations on Occurrence of Radioactive Zinc in Prostatic and Other Human Tissues, Brit. J. Urol. **28:**271-278 (Sept.) 1956.

7. Huggins, C.: Prostatic Secretion, Harvey Lect. (1946-1947) **42:**148-193, 1947.

8. Roberts, K. E.; Randall, H. T.; Philbin, P.; and Lipton, R.: Changes in Extracellular Water and Electrolytes and Renal Compensations in Chronic Alkalosis, as Compared to Those Occurring in Acute Alkalosis, Surgery **36:**599-609 (Sept.) 1954.

9. (*a*) Sierp, M.; Prout, G. R.; and Whitmore, W. F., Jr.: Unpublished data. (*b*) Reference 5.

10. Huggins, C.; Masina, M. H.; Eichelberger, L.; and Wharton, J. D.: Quantitative Studies of Prostatic Secretion: Characteristics of Normal Secretion: Influence of Thyroid, Suprarenal, and Testis Extirpation and Androgen Substitution on Prostatic Output, J. Exper. Med. **70:**543-556 (Dec.) 1939.

11. Prout, G. R., and Knowles, J. O.: Unpublished data.

12. Mawson, C. A., and Fischer, M. I.: Carbonic Anhydrase and Zinc in Prostate Gland of Rat and Rabbit, Arch. Biochem. **36:**485-486 (April) 1952.

13. Gilman, A., and Brazeau, P.: Symposium on Electrolyte Metabolism: Role of Kidney in Acid-Regulation of Base Metabolism, Am. J. Med. **15:**765-770 (Dec.) 1953.

14. Mawson, C. A.: Personal communication to the authors. Reference 2.

INAPPARENT PYELONEPHRITIS—THE MISSING LINK?

Jay P. Sanford, M.D., Dallas, Texas

A significant degree of bacteriuria has been found in some cases to exist in the absence of leukocytes in the urine and also in the absence of such urologic symptoms as dysuria, frequency, and nocturia. Autopsies disclose the presence of pyelonephritis in cases where it had not been recognized ante mortem. For these reasons it is suggested that there must exist an asymptomatic stage in the history of pyelonephritis, intervening between the acute stage and the chronic end-stage. Recognition of the asymptomatic stage depends on the development of reliable and safe techniques for detecting bacteriuria. It is essential if the termination in hypertension and uremia is to be prevented.

Inapparent pyelonephritis occupies a pivotal position in the course of pyelonephritis. Both acute pyelonephritis and chronic end-stage pyelonephritis manifested by uremia and hypertension are generally recognized. The link between these apparent phases is less well appreciated. Pyelonephritis has been found in 6 to 20% of autopsies; yet the clinical diagnosis of pyelonephritis was made in only about one-fifth of these cases.[1] This discrepancy suggests a high incidence of inapparent pyelonephritis in the general population. It is the purpose of this discussion to reemphasize the inapparent phase in the natural course of pyelonephritis and to discuss the clinical recognition of inapparent active pyelonephritis. Recognition of this phase is dependent upon safe methods for detecting bacteriuria. The value of quantitative bacterial counts as an aid in the differentiation of contaminating from significant bacteria in urine cultures and the feasibility of employing "voided" urine specimens obtained from both males and females as screening cultures to facilitate the detection of inapparent pyelonephritis will be presented.

Spectrum of Pyelonephritis

The natural course of pyelonephritis is clinically apparent as a series of separate and unrelated events. The patient is seen by different specialists during each episode of infection, which tends to fragment genuine understanding of the course of renal infection. The discrepancy between the frequency of pathological evidence of active pyelonephritis and clinical evidence of acute pyelonephritis suggests that these separate episodes of acute infection may be linked via an active inapparent phase. Pyelonephritis may then be considered as a disease continuum, illustrated hypothetically in the figure.[2] There is additional clinical evidence which suggests the presence of continued active inapparent renal infection. For example, the so-called pyelitis of infancy usually has been considered as a self-limited illness. Long-term reevaluation has failed to justify this optimism (table 1).[3] A striking feature was the frequency of abnormalities, which included at least one of the following conditions: abnormality on intravenous urography, persistent pyuria, or positive urine cultures. The majority of these patients with residual abnormality were completely asymptomatic at the time of follow-up study.

From the Department of Internal Medicine, University of Texas Southwestern Medical School.

Read before the Joint Meeting of the Section on Pathology and Physiology and the Section on Urology at the 107th Annual Meeting of the American Medical Association, San Francisco, June 26, 1958.

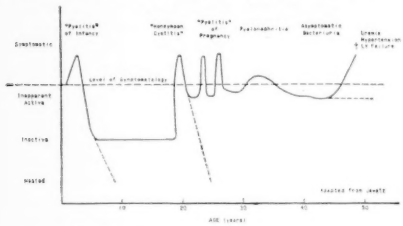
An association between chronic pyelonephritis and arterial hypertension, necrotizing arteriolitis, and uremia was clearly demonstrated by Weiss and Parker.[4] While a direct causal relationship between pyelonephritis and arterial hypertension has not been unequivocally demonstrated, the association is definitely suggestive. The importance of inapparent pyelonephritis as a link between acute renal infection and end-stage pyelonephritis was suggested from the first by Weiss and Parker when they asked the following question: "Are cases of 'silent bacteriurias' benign, or can they cause subsequent hypertension or renal failure? Should they be treated as intensely as those associated with the clinical picture of pyelonephritis?"[4, 5] This question as to the role of inapparent progressive pyelonephritis or "asymptomatic bacteriuria" in the natural history of pyelonephritis has not been clearly defined as yet.

Methods of Recognition

If one accepts the existence of an inapparent active phase as a possible link between episodes of clinically obvious acute pyelonephritis or between acute pyelonephritis and end-stage pyelonephritis, how can this inapparent active phase be detected? Is "silent" or asymptomatic bacteriuria a manifestation of active inapparent pyelonephritis? Evaluation of asymptomatic bacteriuria is dependent on methods for the differentiation of infection from contamination during collection of a urine specimen for culture. The urethra normally contains bacteria in the distal 2 to 3 cm.; hence, the most

meticulous cleansing techniques cannot avoid contamination with organisms from the urethra either in obtaining voided or catheterized specimens.[6]

The usual method of determining the significance of any given bacterial strain has been the demonstration of its constancy in the urine in the absence of specific therapy. This method has the obvious disadvantage of requiring multiple pretherapy cultures, each taken with meticulous care. The delay this necessitates often cannot be afforded. Recently reemphasis has been placed on various techniques utilizing quantitation of the numbers of bacteria per milliliter of urine to facilitate the differentiation of "significant bacteriuria" from contaminants introduced during collection.[7] The most widely employed technique consists of diluting a fresh or freshly refrigerated urine specimen 1 to 1,000 or more times before inoculating solid culture mediums. Various dilution procedures varying from incorporating tenfold serial dilutions of urine into "pour plates" to streaking medium with a standardized loopful of urine may be utilized. These procedures enable the enumeration of the bacteria per milliliter of urine. We currently use the following technique: 0.1 ml. of urine is pipeted into a tube containing 9.9 ml. of sterile distilled water and the contents well mixed. This gives a 1:100 dilution. Then 0.1 ml. of the 1:100 dilution is added to a Petri dish and covered with approximately 10 ml. of melted cooled nutrient agar. The plate is swirled to effect mixing, allowed to solidify, incubated at 37 C overnight, and the number of bacterial colonies counted. The bacterial count represents the number of bacteria in 0.001 ml. of urine. Such techniques have been shown to be feasible in the routine general hospital laboratory.



Natural history of pyelonephritis illustrated hypothetically. Adapted from Jawetz.[2]

The consensus would place the number which distinguishes significant bacteriuria from contamination in the range of 10,000 to 100,000 bacteria per milliliter of urine. Most specimens which are contaminated during collection contain less than 1,000 bacteria per milliliter, whereas specimens obtained from patients with clinically typical acute pyelonephritis contain greater than 100,000 bacteria per milliliter. While the range between 10,000 and 100,000 bacteria per milliliter seems great, Kass[7c] found only 1% of cultures fell into this range. The relative preponderance of bacterial species isolated changes with the degree of bacteriuria. Coagulase negative staphylococci, of which the majority are nonhemolytic and nonpigmented, are commonly found in cultures with less than 1,000 bacterial colonies per milliliter. Aerobacter aerogenes and Escherichia coli occur more frequently in high concentration. These species are considered to be infrequent contaminants. It should be emphasized that the mere presence or absence of any given micro-organism is not an adequate basis for ruling it in or out as a cause of clinical urinary tract infection. A fairly good correlation exists between the concentration of bacteria and microscopic examination of stained smears of urine. Approximately 5,000 to 10,000 viable bacteria per milliliter have to be present before they can be seen on stained smears.[7b] Kass has reported that staining for bacteria is about 80% reliable.[7c]

Results

By the application of such quantitative techniques to the screening of various groups of patients, significant bacteriuria has been demonstrated with considerable frequency (table 2).[8] The variations in frequency are the result, in part, of the type of patient included in the survey. The incidence of significant bacteriuria was found to be 18% in females and 5% in males with diabetes mellitus, 11% in women at term, 23% in women with cystocoeles, and 70% in men on a urological ward.

The clinical and laboratory features observed in a group of patients with "positive cultures" were compared with those observed in a group of patients with "negative cultures" to ascertain whether or not there were clinical indications suggesting relatively asymptomatic bacteriuria.[8c] These observations were made on 100 consecutive admissions to a female general public medical ward. None of the patients had overt acute pyelonephritis. Urinary tract symptomatology consisting of minimal dysuria, frequency, and nocturia was commonly elicited from patients with positive cultures. Yet these symptoms were not present in all patients with positive cultures and were elicited from a considerable number of patients with negative cultures. Routine urinalyses in each group were quite similar. An attempt was made to separate those with negative cultures from those with positive cultures by noting the combination of clinical observations, such as

TABLE 1.—*Prognosis of Pyelitis in Infancy*

Author	No. of Patients	Follow-up, Yr.	Abnormalities, %
Wharton and others[8a]	30	10	60
Woodruff and Everett[8b]	76	5-23	40
Macaulay and Sutton[8c]	27	5	41*

* 5 deaths.

dysuria, frequency, nocturia, and the presence of leukocytes in the urine. Only 1 of 86 patients had this combination in the group with negative cultures; yet only 3 of 14 patients with positive cultures had these findings. It was found that no historical or laboratory evidence allowed separation of patients with positive cultures from those with negative cultures except the quantitative estimation of bacteriuria. Thus, asymptomatic bacteriuria is truly asymptomatic.

Comment

While the over-all incidence of asymptomatic bacteriuria in patients closely approximates the frequency with which pyelonephritis is observed at autopsy, this does not establish a causal relationship and does not answer the question: Is asymptomatic bacteriuria a manifestation of active inapparent pyelonephritis? MacDonald and co-workers [9] recently studied the relationship of bacteriuria to pathological lesions of the urinary tract in 100 unselected autopsies done on adults. The finding of true bacteriuria (defined by them as greater than 100,000 bacteria per milliliter of urine) correlated quite well with the presence of pyelonephritis, and they suggest such a relationship may also obtain during life. Kass [7c] also observed that 40% of patients with asymptomatic bacteriuria during pregnancy will develop apparent acute infection if not given antimicrobial agents. These observations certainly suggest a relationship between asymptomatic bacteriuria and inapparent active pyelonephritis.

It seems apparent that bacteriological study alone can detect these inapparent infections. Bladder catheterization is the commonly accepted technique for obtaining urine from female patients for either examination of the sediment or culture. It has been appreciated that catheterization per se includes some hazard of introducing organisms into the bladder which may be capable of producing urinary tract infections.[10] The incidence of such iatrogenic infection is not precisely known; however, it is probable in 2 to 3% of female patients after catheterization.[11] The disadvantage of this risk must be weighed against overlooking asymptomatic bacteriuria.

Collection of midstream-voided urines combined with quantitative bacterial counting has recently been compared with catheterized urine collections.[12] In a study of 100 consecutive ambulatory and nonambulatory admissions to a female general medical ward "sterile-voided" urine specimens were obtained by ward personnel, which included both graduate and student nurses.[8c] Urine obtained from 61 patients had less than 1,000 bacteria per milliliter, while that from 17 patients contained greater than 100,000 bacteria per milliliter. An "essentially negative" urine culture obtained by voided technique is obviously as meaningful as an "essentially negative" culture obtained by catheterization. Of the 17 patients with large high concentrations of bacteria on voided specimens, 13 had similar numbers of the same bacterial specie on subsequent catheterized specimens.

Kass [7c] has reported that "specimens voided into sterile containers could be obtained from females and from children and used for quantitative study." The correlation between voided specimens with bacterial counts exceeding 100,000 bacteria per milliliter and catheterized specimens is over 95%. The technique of "sterile-voided" urine cultures has been employed routinely at the Boston Lying-In Hospital for the past year and has been found to be feasible as well as satisfactory.[13] Thus, it becomes feasible to screen patients for inapparent pyelonephritis without the risk of introducing infection. However, with preliminary evidence of a significant degree of bacteriuria, either careful repetition of a "sterile-voided" urine collection or catheterization is advisable before undertaking extensive urological or bacteriological diagnostic and therapeutic regimens. Jackson and co-workers [12a] estimate that 5% of patients with low degrees of bacteriuria actually have chronic pyelonephritis. Thus, detection of the abacteriuric phase of inapparent pyelonephritis remains elusive.

TABLE 2.—*Frequency of Asymptomatic Bacteriuria in Hospitalized Patients*

Author	Percentage with Positive Cultures	
	Male	Female
Marple[7a]	---	23
Looguyt[8a]	3	29
Kass[7c]	12	30
	3*	6*
Merritt and Sanford[8c]	---	14
Boshell and Sanford[8b]	---	15

* Outpatients.

Detection of the presence of inapparent pyelonephritis merely opens the door to many important questions to be answered. Are such patients predisposed to subsequent acute apparent infections? Does inapparent pyelonephritis progress to subsequent chronic pyelonephritis with hypertension and renal insufficiency? Does therapy alter the course of inapparent pyelonephritis? Most of these as yet are unanswered. In preliminary observations, Kass [7c] noted that if bacteriuria were eliminated during pregnancy, acute pyelonephritis was not encountered; whereas about 50% of patients with bacteriuria treated with placebo during pregnancy developed overt infection.

Summary

The discrepancy noted between the incidence of significant pyelonephritis demonstrable at autopsy examination and the antemortem diagnosis of pyelonephritis suggests the existence of inapparent

pyelonephritis as a phase in the natural history of pyelonephritis. The over-all incidence of "asymptomatic bacteriuria" fairly closely approximates the frequency with which pyelonephritis is observed at autopsy. Evaluation of asymptomatic bacteriuria is dependent upon bacteriological quantitative estimation of bacteriuria. Clinical history or urinalysis does not aid in detection of bacteriuria. The utilization of a quantitative culture technique enables satisfactory evaluation of voided urine cultures obtained from female patients. This facilitates detection of inapparent infection by eliminating the hazard of introducing infection. The role of inapparent pyelonephritis in the genesis of chronic pyelonephritis and the effect of therapy in altering the course of inapparent pyelonephritis is still unknown.

5323 Harry Hines Blvd. (19).

Drs. B. Boshell, C. B. Favour, J. H. Harrison, and A. D. Merritt and Mrs. F. H. Mao assisted in various phases of these studies.

References

1. Jackson, G. G.; Dallenbach, F. D.; and Kipnis, G. P.: Symposium on Clinical Advances in Medicine: Pyelonephritis: Correlation of Clinical and Pathologic Observations in Antibiotic Era, M. Clin. North America **39:**297-305 (Jan.) 1955.

2. Jawetz, E.: Urinary Tract Infections, DM (Disease-a-Month), Nov., 1954.

3. (*a*) Wharton, L. R.; Gray, L. A.; and Guild, H. G.: Late Effects of Acute Pyelitis in Girls, J. A. M. A. **109:**1597-1602 (Nov. 13) 1937. (*b*) Woodruff, J. D., and Everett, H. S.: Prognosis in Childhood Urinary Tract Infections in Girls, Am. J. Obst. & Gynec. **68:**798-809 (Sept.) 1954. (*c*) Macaulay, D., and Sutton, R. N. P.: Prognosis of Urinary Infections in Childhood, Lancet **2:**1318-1319 (Dec. 28) 1957.

4. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18:**221-315 (Sept.) 1939.

5. Weiss, S., and Parker, F., Jr.: Relation of Pyelonephritis and Other Urinary-Tract Infections to Arterial Hypertension, New England J. Med. **223:**959-967 (Dec. 12) 1940.

6. (*a*) Helmholz, H. F.: Determination of Bacterial Content of Urethra: New Method, with Results of Study of 82 Men, J. Urol. **64:**158-166 (July) 1950. (*b*) Guze, L. B., and Beeson, P. B.: Observations on Reliability and Safety of Bladder Catheterization for Bacteriologic Study of Urine, New England J. Med. **255:**474-475 (Sept. 6) 1956.

7. (*a*) Marple, C. D.: Frequency and Character of Urinary Tract Infections in Unselected Group of Women, Ann. Int. Med. **14:**2220-2239 (June) 1941. (*b*) Sanford, J. P.; Favour, C. B.; Mao, F. H.; and Harrison, J. H.: Evaluation of "Positive" Urine Culture, Am. J. Med. **20:**88-93 (Jan.) 1956. (*c*) Kass, E. H.: Bacteriuria and Diagnosis of Infections of Urinary Tract with Observations on Use of Methionine as Urinary Antiseptic, A. M. A. Arch. Int. Med. **100:**709-714 (Nov.) 1957.

8. (*a*) Loopuyt, L.: Infections of Urinary Tract: Frequency of Urinary Infections, Acta med. scandinav. **125:**245-255, 1946. (*b*) Boshell, B. R., and Sanford, J. P.: Screening Method for Evaluation of Urinary Tract Infections in Female Patient Without Catheterization, Ann. Int. Med. **48:**1040-1045 (May) 1958. (*c*) Merritt, A. D., and Sanford, J. P.: Sterile-Voided Urine Culture: Evaluation in 100 Consecutive Hospitalized Women, J. Lab. & Clin. Med. **52:**463-470 (Sept.) 1958. (*d*) References 7*a* and *c*.

9. MacDonald, R. A.; Levitin, H.; Mallory, G. K.; and Kass, E. H.: Relation Between Pyelonephritis and Bacterial Counts in Urine: Autopsy Study, New England J. Med. **256:**915-922 (May 16) 1957.

10. Beeson, P. B.: Case Against Catheter, editorial, Am. J. Med. **24:**1-3 (Jan.) 1958.

11. References 6*b* and 7*a*.

12. (*a*) Jackson, G. G.; Grieble, H. G.; and Knudsen, K. B.: Urinary Findings Diagnostic of Pyelonephritis, J. A. M. A. **166:**14-17 (Jan. 4) 1958. (*b*) References 7*c*, 8*b* and *c*, and 10.

13. Desautels, R. E.: Personal communication to the author.

MUTAGENIC AGENTS.—Perhaps it will eventually be recognized as one of the most significant medical features of the early 20th century that, as a by-product of more and more powerful therapeutic procedures and the production of chemical substances outside biologic experiences, the normal protective barriers that kept mutagenic agents from the internal organs have been more and more frequently penetrated. Ionizing radiation is the most important, but . . . other agents must be at work, with increasing leukaemic incidence as the only evidence as yet of their presence. It may be only a tiny price that has to be paid for the advantages of a scientific civilization, but it is disquieting and it raises the lurking fear that anything that is increasing the incidence of leukaemia may also be breaking through the other barriers that in the past have protected the germ cells from mutagens. I think one would be wise to pay more attention to leukaemia even than its intrinsic interest and lethality demand just because of the possibility that it is the best indicator one can have of the last and greatest danger to civilization, active and avoidable genetic deterioration. . . . The exposure to physical and chemical mutagens should be reduced as much as possible. This in its turn calls for the recognition of the significant mutagenic agents in an environment always being modified by scientific and technologic development. The importance of ionizing radiation has now been recognized, and one knows how one should act in regard to it. On the chemical side a beginning has hardly been made.—M. Burnet, Leukaemia as a Problem in Preventive Medicine, *South African Practitioner,* January, 1959.

PRACTICAL VALUE OF ANALYSIS OF URINARY CALCULI

Julius H. Winer, M.D., Beverly Hills, Calif.

Classification of urinary calculi depends on comparatively simple chemical tests. Such tests yield valuable clues as to the cause of the lithiasis and the aim of treatment. The pH of urine normally fluctuates daily over a range from pH 4.5 to 7.5. Isohydruria, a narrowing of the range of diurnal fluctuation, is one of the possible causes of lithiasis and is easily remedied by diet and drugs. The list of other possible causes includes a number of conditions that are easily remedied once the cause is identified.

Urinary calculi should be analyzed after their removal or passage from the urinary tract in order to properly manage the future of the patient. Knowing the chemical composition of the calculus gives important information as to what substances are coming down in the urine and gives clues to any causes of recurrent stone formation which may be present. Although this same information may be deduced by other means, such as studies of urinary sediment, blood and urine chemistry studies, urine and blood pH records, and urologic x-ray investigation, the chemical analysis of the stone may give the first exact information and confirms the other studies.

Analysis and Chemical Composition

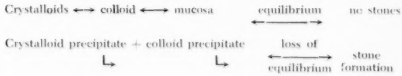
Analysis.—The four common crystalloid compounds in urinary stones [1] are calcium phosphate, calcium oxalate, magnesium ammonium phosphate, and uric acid; less common are calcium carbonate and cystine stones. Mixtures of these salts are common. Sulfonamide calculi are now rare. Many subtypes of common calculi due to variations in physical and chemical structure and many rare constituents are found by petrographic methods of analysis,[2] such as polarized microscopy (spectrography), x-ray crystallography, x-ray microdiffraction, microradiography, and paper chromatography. Traces of bismuth, copper, zinc, lead, silver, manganese, and fluorine have been found. As yet, these biophysical methods and findings are not practical in clinical management of the patient with urinary calculi. The presence of the common crystalloids may be determined by using eight simple spot tests (see table).

Chemical Composition.—The findings of these qualitative tests indicate the compounds which make up the stone. Uric acid and cystine stones are usually pure. Calcium is combined with phosphate, oxalate, or carbonate. A combination of magnesium and ammonium and calcium phosphate (triple phosphate) is found in infected urine. Chemical composition may direct attention to some of the exogenous and endogenous influences on the absorption, excretion, and precipitation of the crystalloids. This can be associated with knowledge of the mechanisms of stone formation.

Mechanism of Stone Formation

The urinary crystalloids are present in a supersaturated solution of electrolytes and nonelectrolytes controlled by presence of suspended colloids which also maintain a surface tension equilibrium with the urinary tract mucosa.[3]

Although there is constant crystallization and resolution of crystalloids, any disturbance of the surface tension equilibrium of the crystalloid-colloid interface or the urine-mucosa interface may cause a precipitation and conglomeration of mucopolysaccharides and mucoprotein nidus or matrix covering and preventing resolution of precipitated crystalloids. A formula of normal equilibrium and a formula of stone formation is as follows:



The known exogenous and endogenous causes of stone formation affect the equilibrium at various points of the formula. They are frequently interrelated. The seven types of tendencies to calculus formation are as follows: (1) metabolic disturbances (anabolic and catabolic), uricaciduria (gout, polycythemia), oxaluria, and cystinuria; (2) endocrinopathy: hyperparathyroidism; (3) urinary obstruction (stasis); hydronephrosis; (4) infection: urea-splitting bacteria; (5) mucosal metaplasia; avitaminosis A; dietary deficiency; Randall's plaques; (6) extrinsic: dehydration; dietary excess (milk drinkers); drug excess (alkalizers, purine drugs); recumbency; chemotherapy; and (7) isohydruria [5]: loss of wide acid-alkaline tides and fixation of urinary pH. Although any one of these disturbances may be present without the formation of calculi, two or more are associated with most instances of stone formation, and the isohydruria is the condition most often found in combination with the others.

From the Department of Surgery (Urology), University of California Medical Center, Los Angeles.

Read before the Joint Meeting of the Section on Pathology and Physiology and the Section on Urology at the 107th Annual Meeting of the American Medical Association, San Francisco, June 26, 1958.

Isohydruria is the fixation of urinary pH within a narrow range throughout most of each 24-hour cycle instead of a normal, widely fluctuating acid-alkaline tide (pH 4.5 to pH 7.5). The pH figures as noted on nitrazine paper have been practical for clinical use. Bridges and Mattice [4] have shown that the diurnal acid-alkaline pH curve follows as regular an individual specific pattern as do human fingerprints. During stone formation, there is fixation of pH levels with characteristic but only mild fluctuations of that individual's normal curve. Reynolds [5] suggested the term "isohydruria" for this condition whether it be in the acid, alkaline, or neutral range. Isohydruria of acid type (pH 4.5 to 5.5) is associated with uric acid precipitation; alkaline isohydruria (pH 7.0 to 7.5) promotes precipitation of calcium phosphate calculi; and mildly acid to neutral fixation (pH 5.5 to 6.0) favors calcium oxalate stones.

*Spot Tests to Determine Presence of Common Crystalloids in Urinary Calculi**

Chemical	Method	Finding
1. Uric acid	Powdered stone; 1 drop 20% sodium carbonate; 2 drops uric acid reagent	Prompt deep blue color (pale blue is negative)
2. Phosphate	Powdered stone†; 4-5 drops ammonium molybdate (3.5 Gm. in 75 cc. water and 25 cc. concentrated nitric acid)	Distinct yellow precipitate (may be warmed)
3. Oxalate	a. Powdered stone; 2-3 drops 10% HCl; if no effervescence, cool and add pinch of manganese dioxide; do not mix	Tiny bubbles of gas explosively released from bottom
	b. Char small fragment on spatula and add 2 drops 10% HCl‡	Foaming effervescence
4. Carbonate	relatively large sample of powdered stone; 8-10 drops 10% HCl (save for 5, 6, 7a)	Foaming effervescence
5. Calcium	Acid extract§: 2-3 drops 20% NaOH	Fine white precipitate or film from oxalate stones; dense precipitate from phosphate stone
6. Magnesium	Acid extract: 2-3 drops of 20% NaOH; 2-3 drops "M" (p-nitrobenzene-azoresorcinol, 1 mg. in 100 cc. normal NaOH)	Reddish-purple reagent slowly becomes definitely blue (precipitate forms)
7. Ammonium	a. Acid extract: 2-3 drops of 20% NaOH; 2-3 drops Nessler's solution	Yellowish orange precipitate
	b. powdered stone; 2-3 drops Nessler's solution	Yellowish orange precipitate
8. Cystine	a. Powdered stone; 1 drop NH_4OH; 1 drop 5% NaCN (wait 5 minutes); 2-3 drops 5% sodium nitroprusside	Beet-red color; on standing may fade to orange-red
	b. Char over flame‖	Hydrogen-sulfide odor

* Adapted from Winer and Mattice.[3]

† Performed on a micro slide, it is much easier to see the precipitate. (The other tests are best performed on an artist's spot plate on which several calculi can be analyzed simultaneously.)

‡ Simple alternate methods require heat to char the stone fragment in a platinum spatula. Technical errors can be avoided by washing surface and taking samples by scraping various layers and nucleus with a knife.

§ With use of a medicine dropper, tip plugged with a wisp of cotton, acid extract from no. 4 is taken up, cotton removed, and filtrate divided for nos. 5, 6, and 7.

Isohydruria is only a single factor influencing precipitation of the crystalloids and their colloid matrix by disturbance of equilibrium at colloid-crystalloid interface. Isohydruria may be of intrarenal origin (excretory enzymes, electrolyte excretion) or may be due to extrarenal causes, such as stasis or infection (residual urine prevents widely changing pH as a hydronephrosis and vesical neck obstruction. Infection may give a constant alkaline pH fixation). Isohydruria has been found to be temporary in some patients and permanent in others. The permanent types usually show pure calculi, whereas the temporary types often show mixed types of calculi and will on occasion have wider fluctuations of pH.

Components of Calculi

Considerable information is known regarding absorption, excretion, and precipitation of crystalloids in calculi.[6] Further investigation of the colloid factors may yield practical tests of chemical significance in the future, but only the crystalloid factors have practical clinical significance at this time.[7]

Calcium.—Although the diet contains both organic and inorganic calcium, only inorganic calcium is absorbed, probably in the upper small intestine. Calcium absorption is improved by an acid reaction and enhanced by digestion of sugars which produce intestinal acidity. Vitamin D increases calcium absorption. Dietary fat lessens calcium absorption in a high-calcium, low-phosphorus diet, but calcium absorption is increased by dietary fat with a low-calcium, high-phosphorus diet. Calcium chloride, calcium lactate, and calcium gluconate are soluble and easily absorbed, whereas the phosphate is poorly soluble and resists absorption. Protein increases calcium absorption by forming soluble calcium-amino acid complexes.

Milk and cheese are the most important calcium-containing foods. Hard water and some vegetables, especially carrots, have readily absorbable calcium, whereas spinach, rhubarb, and other high oxalate vegetables diminish calcium absorption.

Calcium is excreted into the lower small intestine and into the urine. About 150 mg. of calcium are excreted daily in the urine, but this varies widely even with a fixed diet. A positive "calcium balance" occurs when the quantity of calcium absorbed is greater than the amount excreted in the urine and bowel, occurring during growth, pregnancy, after calcium starvation, or after testosterone administration. Negative calcium balance occurs in rickets, sprue, osteomalacia, and hyperparathyroidism, during starvation, and with prolonged recumbency.

Phosphorus.—Normal urinary phosphorus occurs mostly as sodium phosphate, some as potassium phosphate, and less as calcium and magnesium phosphates; the latter salts precipitate in alkaline urine. Ingestion of alkali may cause cloudy urine (phosphaturia) by facilitating the precipitation of insoluble calcium and magnesium phosphates. The levels of urinary phosphates increase during starvation, during severe muscular exercise, and after the administration of a high-protein diet, calcium and ammonium chlorides, or parathyroid extract (Parathormone). The urinary phosphate levels diminish during pregnancy, alkalosis, renal insufficiency, and tetany and with certain bone diseases.

Calcium Phosphate Calculi.—Calcium phosphate calculi occur with excess milk intake, excess alkali intake (ulcer therapy), stasis, recumbency, avita-

minosis A, hypervitaminosis D, isohydruria of a moderately alkaline type, and dehydration. In the presence of urea-splitting bacterial infection, mixed calcium phosphate and magnesium ammonium phosphate calculi occur.

Calcium phosphate calculi are associated with bone disease.[8] Hyperparathyroidism (generalized osteitis fibrosa cystica) shows hypercalciuria with precipitation of insoluble calcium phosphate in the renal pelvis, the renal parenchyma, and the other acid-excreting tissues (stomach and lungs). In osteitis deformans (Paget's disease of bone) 10% of patients have calculi. Osteoporosis with hypercalciuria occurs in the postmenopausal state, especially after surgical castration. Such hypercalciuria also is seen in senility, disuse atrophy, and decalcification of immobilization, treatment with estrogens, malnutrition, Cushing's syndrome (rare), ACTH treatment, cortisone treatment, acromegaly, multiple myeloma, hypervitaminosis C, and Fanconi syndrome (aminoaciduria).

Oxalates.—Oxalates are normally present in the urine and blood. Reliable methods of determination of blood-oxalate levels are not generally available. The normal urinary oxalate is 20 to 47 mg. in 24 hours. Urinary oxalate is supersaturated from two and one-half to three and one-half times its normal solubility at pH 5.5.[9]

Blood oxalate develops from dietary oxalate absorption, from oxalate formed by bacterial activity in the intestine, and as an intermediate product during endogenous tissue metabolism. Urinary oxalate excretion persists on an oxalate-free diet and during starvation. Spinach, rhubarb, and asparagus contain large amounts of oxalate, and many of the common fruits and vegetables have it in smaller amounts. The oxalate may be present as insoluble calcium oxalate, as soluble sodium and potassium oxalates, and, in very slight amounts, as oxalic acid. Hyperchlorhydria increases and achlorhydria decreases oxalate absorption. The soluble oxalate in the food may be absorbed; milk, with its high calcium content, prevents absorption of soluble dietary oxalates by converting them into insoluble calcium oxalate.

Tissue glycogen is a probable source of oxalic acid; oxalates are produced when carbohydrates are incompletely metabolized as in diabetes and liver disease. Oxalates may also result from the digestion of the proteins and fat. Although the oxalic acid is relatively inadequately traced in endogenous metabolism, studies show that administration of glucose, ethylene glycol, glyoxal, and glycolic acid increase oxalic acid in the urine. (Mandelic acid splits into phenol or glycocolic acid, the latter being a precursor of oxalic acid.)

Calcium oxalate calculi occur with oxaluria due to dietary excess, possible dietary deficiencies, possible metabolic errors, isohydruria at pH 5.5 to 6.0, associated with hypercalciuria, stasis, and dehydration. Oxalate metabolism and stone formation are poorly known mechanisms. Oxalate calculus formation due to acetazolamide (Diamox) has been noted, the carbonic anhydrase inhibition causing fixation of urine pH. Oxalate calculi are formed frequently with Boeck's sarcoid.

Hammarsten[10] believes that endogenous oxalate is an undesired by-product due to a metabolic disturbance resulting from magnesium deficiency. High levels of urinary magnesium are said to increase calcium oxalate solubility. In 1937, Hammarsten produced oxalate stones in rats with a low magnesium diet; the stones were larger and more numerous in the absence of vitamins and a diminution of calcium in the diet caused an increased elimination of calcium in the urine; this was more marked when the animal was deficient in vitamin D, thereby lowering absorption of calcium from the intestine. She believed that under such circumstances calcium is mobilized from the bones in excess of requirements, the excess being excreted in the urine. Stones were formed even if the diet was free of oxalate, but additional oxalate in the diet caused an increase in stone formation. The highest incidence of oxalate stones occurred with a low magnesium, high oxalate, low vitamin, acid ash diet. The resulting acid-sterile urine showed a decreased magnesium content and an increase of calcium oxalate calculi. If the diet was of alkaline ash type, calcium phosphate calculi were produced.

Uric Acid.—Exogenous uric acid is derived from dietary purines, while the endogenous portion is derived from the degradation of nucleoproteins during tissue catabolism, as well as from free mononucleotides found in muscles and glands. The liver is the probable site of destruction of 30 to 70% of the uric acid production, the remaining being excreted in the urine as free uric acid and as sodium potassium and ammonium urates. The output of urinary uric acid is 0.5 to 1.0 Gm. per 24 hours.

Uric acid calculi are usually pure (rarely urates) and are found with uricosuria, hyperuricemia, mild polycythemia (which is noted in many patients with uric acid calculi and uric acid showers), polycythemia vera, stress polycythemia,[11] lymphomas (without and especially with treatment), exogenous dietary excess, or purine drug therapy (theophylline), acid isohydruria, and hepatic disease. Relatively more bladder stones are of uric acid composition than are kidney stones. However, uric acid kidney stones may elude diagnosis and removal due to their radiotranslucency.

Comment

After a calculus is obtained from the patient, it is important to eliminate any known causes of stone formation. Chemical analysis may give information as to the specific causes of formation of each type of stone and as a guide to preventing further precipitation of this compound in the urine.

Attempts should be made to prevent excessive absorption, endogenous formation, concentrated excretion and diminished solubility. Where the

etiology is unknown, the chemical composition indicates the type of isohydruria which permits each particular crystalloid to be precipitated with its associated matrix. Isohydruria may be changed by proper utilization of drug and dietary means. Intermittent alkalinization may be achieved through use of palatable alkalis or alkaline ash foods (cantaloupe is the food of greatest effect). Intermittent acidification is achieved with sodium acid phosphate, ammonium chloride, betaine hydrochloride, or acid ash foods. Cranberry juice was found to be the most potent dietary acidfier in a study of a group of paraplegics with urinary calculi. The occasional need for rapid diuresis led to use of various diuretics, but beer gave an adequate rapid diuresis in most cases.

Summary

Simple spot-test chemical analysis of urinary stones gives practical information of value for management of the patient with urinary calculi.

9915 Santa Monica Blvd.

References

1. Winer, J. H., and Mattice, M. R.: Routine Analysis of Urinary Calculi: Rapid, Simple Method Using Spot Tests, J. Lab. & Clin. Med. **28:**898-904 (April) 1943.
2. Prien, E. L.: Studies in Urolithiasis: Relationships Between Pathogenesis, Structure and Composition of Calculi, J. Urol. **61:**821-836 (May) 1949. Prien, E. L., and Frondel, C.: Studies in Urolithiasis: Composition of Urinary Calculi, ibid. **57:**949-994 (June) 1947.
3. Butt, A. J.: Etiologic Factors in Renal Lithiasis, Springfield, Charles C Thomas, Publisher, 1956.
4. Bridges, M. A., and Mattice, M. R.: Control of Urine Reaction, Am. J. M. Sc. **200:**84-96 (July) 1940.
5. Reynolds, T. B.: Personal communication to the author.
6. Mattice, M. R.: Chemical Procedures for Clinical Laboratories, Philadelphia, Lea & Febiger, 1936.
7. Herman, J. R.: Recent Advances in Study and Treatment of Urolithiasis, New York J. Med. **57:**2844-2852 (Sept. 1, pt. 1) 1957.
8. Albright, F., and Reifenstein, E. C.: Parathyroid Glands and Metabolic Bone Disease: Selected Studies, Baltimore, Williams & Wilkins Company, 1948.
9. Lassen, H. K.: Formation of Urinary Calculi, J. Urol. **50:**110-120 (July) 1943.
10. Hammarsten, G., in Butt.[3]
11. Rubinstein, M.: Personal communication to the author.

FIBRINOLYSIS IN UROLOGIC PATIENTS

Louis J. Lombardo Jr., M.D., Los Angeles

Severe hemorrhages after prostatic surgery may be due to a fibrin-dissolving protease found in normal prostatic tissue. The intravascular release of enzyme activators from the prostate may also explain the chronic fibrinolysis that occurs in metastatic carcinoma of the prostate. Experiments in vitro showed that the activity of these enzymes can be opposed by inhibitors. The effectiveness of two preparations of toluidine blue as inhibitors was convincingly shown by observations of plasma fibrinogen levels in 3 groups of 30 patients undergoing prostatectomy. One group received an oral preparation, the second, a parenteral preparation. The third group served for comparison. Liquefaction of extravasated blood in the prostatic fossa was found to be a characteristic phenomenon, but the question is raised whether this may be an essential part of some reparative process. Two case histories illustrate the occurrence and treatment of hemorrhage after prostatectomy.

Acquired fibrinogenopenic states occur rarely in urologic practice. It is perhaps for this reason that this hemorrhagic diathesis has not been recognized more frequently. Most physicians agree that fibrinolysis is associated with urologic cases of hypofibrinogenemia. The fibrinolytic systems, when completely understood, will probably rival in complexity the process of blood coagulation.

A proteolytic enzyme system is present in human plasma (fig. 1). Active enzyme can be prepared from the globulin fraction and an inhibitor from the albumin. The active enzyme plasmin (fibrinolysin) will act on a variety of such substrates as fibrin, fibrinogen, thrombin, prothrombin, casein, and gelatin. Since the enzyme system is not fastidious, it is frequently classified as proteolytic rather than fibrinolytic. The enzyme is derived from a precursor, plasminogen (profibrinolysin). The conversion of plasminogen to plasmin may be caused by the alarm reaction with such stress as severe physical trauma, shock, hemorrhage, burns, and fear. Plasminogen

From the Department of Urology, University of Southern California School of Medicine, the College of Medical Evangelists, and Los Angeles County Hospital.

Read before the Joint Meeting of the Section on Pathology and Physiology and the Section on Urology at the 107th Annual Meeting of the American Medical Association, San Francisco, June 26, 1958.

may be activated as a result of release into the circulation of tissue activator substance and by the activity of bacteria.

A proteolytic enzyme is present in normal prostatic tissue. Tagnon and associates [1] first reported the presence of this fibrinolysin. These investigators considered this to be the fibrinolytic enzyme originally described as present in the prostatic fluid by Huggins and Vail.[2] This fibrinolysin is similar in action but probably not identical to the plasmin in normal serum.

It may be postulated that fibrinolysis associated with prostatic surgery or the chronic fibrinolysis occurring in metastatic carcinoma of the prostate may be entirely due to intravascular release of the prostatic proteolytic enzyme or due to intravascular release of enzyme activators from the prostate triggering the plasmin system. The pathogenesis in prostatic surgery may conceivably be the general alarm reaction with subsequent activation of plasminogen. It is possible that both the plasmin and prostatic systems are activated.

Studies

The fibrinolytic activity of the prostatic enzyme can be demonstrated in vitro by the fibrin plate method.[3] Purified bovine or human fibrinogen placed on Petri dishes is converted to fibrin by the addition of thrombin. Drops of test preparations are placed on the fibrin plates. Lysis produces a spreading zone of liquefaction, and the area of this, related to time, gives a quantitative measurement. Unheated fibrin plates contain plasminogen as a contaminant and thus are lysed by plasminogen-activators, such as tissue kinases. Plasminogen in such plates may be destroyed by heat denaturation.[4] The zone of liquefaction produced on a heated fibrin plate by an extract of prostatic tissue therefore represents lysis by the prostatic enzyme.

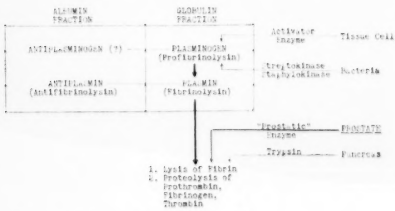


Fig. 1.—Schema of proteolytic enzymes.

Figure 2 shows a heated fibrin plate incubated with benign prostatic tissue. An extract of malignant prostatic tissue incubated on a heat-denatured fibrin plate gives a larger zone of liquefaction, indicating greater fibrinolytic activity (fig. 3).

In vitro studies were undertaken to find inhibitors of the prostatic fibrinolytic enzyme. Two inhibitors were found to be effective in fibrin plate tests, toluidine blue and Klot. Klot is a parenteral preparation of 7% *n*-butyl alcohol with 0.002% toluidine blue in isotonic sodium chloride solution. A test

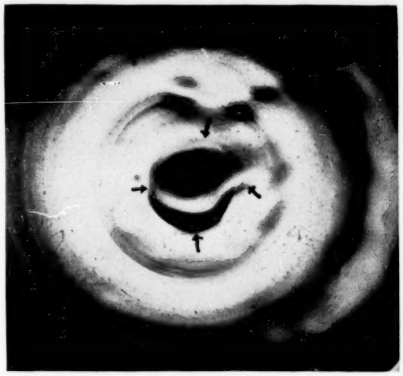


Fig. 2.—Heat-denatured fibrin plate incubated with extract of benign prostatic tissue, showing zone of lysis.

drop of malignant prostatic tissue incubated on a heated fibrin plate prepared with toluidine blue liquefied a small zone of fibrin (fig. 4). The small zone of dissolution indicates inhibition of lysis. A heated fibrin plate prepared with the addition of Klot was incubated with malignant prostatic tissue (fig. 5). A small zone of liquefaction indicates inhibition of lysis.

In acute cases of the prostatic fibrinolytic diathesis, the proteolytic enzyme acts to destroy fibrinogen, accelerator globulin, and prothrombin. A clinical survey was undertaken to evaluate the fibrinogen levels during transurethral prostatectomy. Plasma fibrinogen levels were determined preoperatively and one hour and four hours postoperatively in three groups of 30 patients having transurethral prostatectomies. The first group, the controls, received no special medicaments; the second group received 200 mg. of Blutene, an orally given toluidine blue preparation, 12 hours before surgery; and the third group was given Klot intravenously at the start of resection in a dosage of 1 ml. per 15 lb. of body weight. There were five cases of malignant prostatic carcinoma in each of the three groups.

In the control group the average drop in fibrinogen level from the preoperative period to four hours postoperatively was 20.3%, in the toluidine blue group 11.2%, and in the Klot group 6.3%. More striking is the observation that in 6 of the 30 sub-

jects in the control group the fibrinogen level dropped below the low of accepted normal, 250 mg.%. In one of the six it dropped to zero, or afibrinogenemia. In the groups treated with toluidine blue and Klot, none of the fibrinogen levels postoperatively were below normal.

Fig. 3.—Heat-denatured fibrin plate incubated with extract of malignant prostatic tissue, showing large zone of lysis.

In recent studies, I have attempted to study the fibrinolytic activity of the prostatic fossa after prostatectomy. I thought that prostatic fibrinolysin may cause delayed or secondary hemorrhage by the premature dissolution of hemostatic blood clots before permanent repairs occur. Such hemorrhages would be postulated to occur more frequently after transurethral resection of adenocarcinoma of the prostate, since malignant prostatic tissue shows greater lytic activity. The problem of postprostatectomy hemostasis and hemorrhage is not limited to transurethral resections of carcinoma of the prostate. Conceivably, clot dissolution may occur after enucleation of a benign adenoma.

Figure 6 illustrates the method of collection of blood from the prostatic fossa after prostatectomy. A three-way urethral catheter is employed postoperatively. The catheter's irrigating lumen is plugged at the catheter tip and a hole made in the irrigating channel proximal to the retention balloon at a position corresponding to the prostatic fossa. Blood may be suctioned from the prostatic fossa postoperatively through this revised irrigating channel. There has been considerable variation in the amount of blood aspirated from the prostatic fossa. During periods of collection for blood determinations and evaluation of lytic activity, mild traction has been placed on the catheter to seat the catheter balloon against the bladder neck. This avoids contamination of collections by urine. Blood hematocrit value and hematocrit value of the collected fossa blood are determined for comparison to assure that dilution by urine of the fossa blood has not occurred.

In a group of five patients subjected to suprapubic prostatectomy, fibrinolytic activity was present in three immediately after operation. No clotting of the fossa blood was observed, and in all no fibrinogen was detectable. Lysis was demonstrated in three cases by the fibrin plate test and the lysis time of thrombin-clotted plasma. Complete lysis of blood plasma by fossa plasma in a thrombin-clotted system occurred in 24 hours. In a second group of five patients subjected to suprapubic prostatectomy and treated preoperatively with toluidine blue, no fibrinolytic activity was detected. Accurate fossa fibrinogen level determinations were not possible because of blood clots in the samples. Fibrinolytic activity was not present in the general circulation of these cases.

With present knowledge it is difficult to assess whether this fibrinolytic activity localized to the prostatic fossa is of physiological or pathological significance. Liquefaction of clotted blood is known to occur early in closed spaces, such as hematoceles and hemothorax. Alteration of this possibly physiological proteolytic activity in the prostatic fossa may be detrimental to normal healing.

Report of Cases

The cases of acute fibrinolysis observed on the urologic service have occurred mainly during or after transurethral resection. Fibrinolysis has been

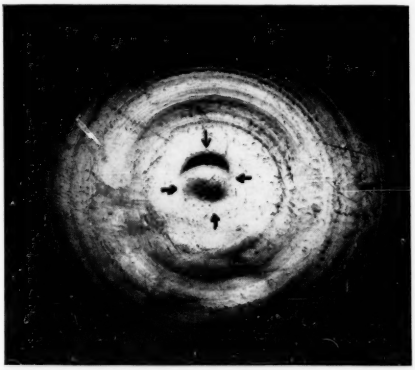


Fig. 4.—Heat-denatured fibrin plate prepared with toluidine blue and incubated with malignant prostatic tissue, showing inhibition of lysis.

observed in resections of benign and malignant prostates. This hemorrhagic diathesis has occurred in resections of unsuspected malignant prostates, known malignant prostates without previous hormonal therapy, and known malignant prostates

during adequate hormonal therapy. Chronic fibrinolysis or instances in which fibrinolysis proceeds slowly has been observed in disseminated prostatic and bladder carcinoma.

The following case demonstrated acute fibrinolysis after transurethral resection of malignant prostatic carcinoma while the patient was on hormonal therapy.

Case 1.—A 76-year-old man entered the hospital because of symptoms of urinary obstruction. Twelve years preceding admission a transurethral resection of the prostate was performed for obstructing adenocarcinoma of the prostate. The patient had been maintained on estrogen therapy for the 12 years. On examination the testicles were atrophic and the prostate small and clinically malignant. An x-ray survey of the bones revealed no evidence of metastases. The serum acid phosphatase level was 6.7 King-Armstrong units. A transurethral resection of the prostate was performed without incident. Four hours postoperatively profuse bleeding from the catheter, without clots, was noted. The blood-clotting time was five minutes, and complete lysis of the clot occurred in one hour. The plasma fibrinogen level was 39 mg.%. Five units of whole blood, 5 Gm. of fibrinogen, and 20 ml. of Klot were administered. Nine hours postoperatively the hemorrhage was controlled. The next day, the blood-clotting time was 5 minutes and there was no clot lysis in 24 hours. The patient was discharged on the sixth postoperative day.

The following patient showed acute fibrinolysis after transurethral resection of benign prostatic tissue.

Case 2.—A 56-year-old man was admitted to the hospital because of symptoms of urinary obstruction. Early during transurethral resection of the prostate the capsule was perforated. The surgeon completed the resection while bleeding continued from the site of perforation. A total of 19 Gm. of benign prostatic tissue was resected. The estimated blood loss at surgery was 800 ml. The patient returned to his room with a stable blood pressure with whole blood being given intravenously. One hour postoperatively profuse bleeding from the catheter, without clots, was noted. Subcutaneous hemorrhages developed on both upper extremities. The blood-clotting time was six minutes, and there was complete clot lysis in two hours. The plasma fibrinogen level was 100 mg.%, and the platelet count was normal. Therapy included 4 units of whole blood, 2 Gm. of fibrinogen, and 25 ml. of Klot given intravenously. Eight hours postoperatively the bleeding was controlled, the plasma fibrinogen level was 220 mg.%, and no clot lysis was observed in 24 hours.

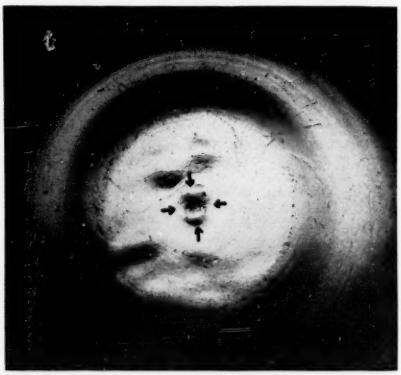


Fig. 5.—Heat-denatured fibrin plate prepared with Klot and incubated with malignant prostatic tissue, showing inhibition of lysis.

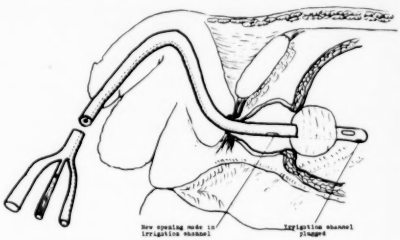


Fig. 6.—Method of collecting blood from prostatic fossa after prostatectomy with revised continuous irrigation catheter.

Diagnosis

The first requisite for establishing the diagnosis of fibrinolysis as a cause of abnormal bleeding is the consideration of its possible existence. Generalized ooze may be noted in the prostatic fossa during transurethral resection. I have noted the delayed occurrence of the lytic syndrome up to six hours postoperatively. Bleeding via the urethral catheter may suddenly change from pinkish or dark old blood to bright red drainage. Usually the bright red blood from the catheter is without blood clots. Sites of fresh punctures in the skin for medication bleed profusely. The skin puncture for spinal or caudal anesthesia may bleed. Subcutaneous and submucosal hemorrhages are noted.

There are many methods of studying fibrinolysis. From the point of view of the clinician, observation of the blood clotting and the future integrity of the clot is both a diagnostic test and also helpful in following the effectiveness of therapy. Venous blood is allowed to clot in a glass test tube at 37 C. The clot is observed from time to time. If lysis occurs, the red blood cells become free and sink to the bottom of the tube, leaving a top layer of serum. In severe cases, the clot may lyse very rapidly after clotting of blood or there may even be no clot formation whatever. The activity of the fibrinolytic enzyme is in direct proportion to the time required for the lysis of the clot.

It is important to remember that clot lysis may be more apparent than real in hypofibrinogenemia. Blood which has a very low concentration of fibrin-

ogen forms a temporary solid clot which is unable to hold together the mass of red blood cells as it retracts. The small retracted mass of fibrin that ultimately remains is masked by a mass of cells, thus making it appear that liquefaction of the whole clot has occurred. Fibrinogen level and prothrombin time determinations and a platelet count are helpful in establishing an accurate diagnosis.

Treatment

In acute fibrinolysis immediate and vigorous measures must be taken. Shock may result in massive activation of fibrinolysin. With further destruction of coagulation proteins, more bleeding takes place and the shock state deepens. Death results unless such a vicious cycle is interrupted. Reference to figure 1 helps to understand the rationale of therapy. Whole blood is essential for rapid replacement and maintenance of blood volume. Whole blood acts upon the abnormal plasma proteolytic activity both directly and indirectly. The direct action is in the supplementation of the patient's plasma with the antifibrinolysin of the albumin fraction. A disadvantage of whole blood is its normal content of profibrinolysin and fibrinolysin of the globulin fraction. With more profibrinolysin available to the patient's enzyme activating system, the proteolytic activity is augmented. The indirect action of whole blood on fibrinolysis is in the supplementation of substrate in the form of fibrinogen, prothrombin, and other coagulation factors. The prevention of shock is probably the most important single indication for blood transfusions in acute fibrinolysis.

Administration of human serum albumin is a direct attack, for it is in the albumin fraction of blood that antifibrinolysin resides. Fibrinogen supplies large amounts of substrate to expend the lytic enzyme and also restores the clotting mechanism. I have alternated 1 Gm. of fibrinogen and 100 ml. of albumin every half hour until there is clinical lessening of bleeding.

Toluidine blue or Klot has been given intravenously for inhibition of circulating lysin. The dosage of toluidine blue found effective is 100 mg. and of Klot 1 ml. per 15 lb. of body weight. Toluidine blue must be diluted to 100 ml. in a vehicle such as glucose and water.

Stefanini and Gendel [5] have reported satisfactory control of the bleeding tendency of disseminated prostatic carcinoma by the administration intramuscularly of ACTH (80-120 units daily in divided doses) or cortisone (150-200 mg. daily in divided doses) until bleeding is arrested. The chronic fibrinolysis of disseminated prostatic carcinoma can often be controlled by stilbestrol therapy. As remission sets in and dissemination of the prostatic tissue is reduced, the bleeding tendency regresses and fibrinolysis disappears.

Comment

It is probable that fibrinolytic activity developing spontaneously in patients who have undergone transurethral resection is due to release into the blood stream of prostatic proteolytic enzyme. Further resection, with open venous sinuses or capsular perforation, provides possible sites for entry into the circulation of prostatic proteolytic enzymes or prostatic tissue activators to trigger the plasma enzyme system. Further evidence for this is the observation that men undergoing transurethral resection of bladder tumors maintain essentially constant plasma fibrinogen levels in the postoperative period. A possible deduction from this is that manipulation or massage of the prostate by a sheath riding over the prostate is not sufficient for intravascular release of prostatic proteolytic activators or enzymes. Further studies of localized prostatic fossa fibrinolytic activity may lead to remedies of the problem of postprostatectomy bleeding and secondary hemorrhages.

Summary

Fibrinolysis in prostatic surgery may be due to intravascular release of the prostatic proteolytic enzyme or of enzyme activators from the prostate triggering the plasmin system. Two prostatic fibrinolytic enzyme inhibitors, toluidine blue and Klot (a parenteral preparation of 7% *n*-butyl alcohol with 0.002% toluidine blue in isotonic sodium chloride solution), were found effective in in vitro and in vivo studies. Acute fibrinolysis after transurethral resection was demonstrated in two surgical patients, one with benign prostatic tissue and one with malignant prostatic carcinoma while on hormonal therapy. Observation of the blood clotting and the subsequent integrity of the clot is a diagnostic test and is also helpful in following the effectiveness of therapy. In acute fibrinolysis, immediate and vigorous measures must be taken.

1801 Wilshire Blvd. (57).

The toluidine blue (Blutene) used in this study was supplied by Abbott Laboratories, North Chicago, Ill. Klot, hemostatic injection, code 71A-47, was supplied by the Warren-Teed Products Company, Columbus, Ohio.

References

1. Tagnon, H. J.; Whitmore, W. F., Jr.; and Shulman, N. R.: Fibrinolysis in Mestatatic Cancer of Prostate, Cancer **5**:9-12 (Jan.) 1952.

2. Huggins, C., and Vail, V. C.: Plasma Coagulation and Fibrinogenolysis by Prostatic Fluid and Tripsin, Am. J. Physiol. **139**:129-134 (May) 1943.

3. Astrup, T., and Müllertz, S.: Fibrin Plate Method for Estimating Fibrinolytic Activity, Arch. Biochem. **10**:346-351 (Oct.) 1952.

4. Lassen, M.: Heat Denaturation of Plasminogen in Fibrin Plate Method, Acta physiol. scandinav. **27**:371-376, 1953.

5. Stefanini, M., and Gendel, B. R.: Influence of Fibrinolysin on Survival "in Vivo" of Various Coagulation Factors and Favorable Effect of Cortisone in "Fibrinolytic Purpura," abstracted, Clin. Res. Proc. **1**:5 (April) 1953.

PLANNED DEVELOPMENT OF LATENT ANAL SPHINCTER

J. James Duffy, M.D., Los Angeles

Unsatisfactory attempts to correct an imperforate anus in a boy at birth were followed by progessive difficulty in defecation until, at the age of 9 years, fecal impaction reached the spenic flexure and colostomy became necessary. Subsequent examination of the remaining fistulous anal tract suggested that restoration of continence might still be possible. This was accomplished at the age of 12 by carefully planned plastic surgery in two stages. The second stage, in which the colostomy was closed, was carried out only after the patient had acquired and demonstrated satisfactory sphincteric control by carefully graduated, highly disciplined exercises, with use of a perineometer and water pressure. Observations seven years after the operation show that the patient is active in athletics and has made an excellent scholastic and social adjustment.

This presentation has for its object the demonstration of a plan to accomplish the reconstruction and development of a workable anal sphincter, many years after birth, for patients born with imperforate anus and helped at the time of birth by colostomy. As the plan unfolds it will be seen to involve a composite concept of the embryology, the myoneural mechanism latent in the anal plate, reconstructive surgery, a highly disciplined regimen of muscle exercises in conjunction with counter-pressures, and finally the restoration of bowel continuity and abolition of the colostomy. The principles may be applied in other situations.

The first case of an attempt of this kind was reported in THE JOURNAL in 1951.[1] As a progress note on that case it is to be noted that since the definitive surgery in 1949, the patient has had no dilatations and no dietary restrictions and fully controls his bowel movements. He is happily married and has a family; he is fully employed and carries standard rate life insurance. In short, he leads a normal life.

The present case, however, presented a slightly different problem. As a result of the encouragement and experience gained from the first case, I believe the present plan to be an improvement.

Report of a Case

On June 18, 1951, a father brought his 12-year-old son for examination and opinion. The complaint was a permanent colostomy and foul-smelling anal sinus.

History.—The patient was born May 12, 1939, and weighed 3,856 Gm. (8.5 lb.); delivery was normal. Immediately it was noted that he had a totally imperforate anus, probably a Ladd type 3,[2] but there could be located a dimple of faint outline. Within two hours, through this dimple, a surgical opening was made and dilatation was done. In spite of strong laxatives, enemas, and repeated dilatations he remained at all times very constipated. Stricture was thought to be the problem, but by 9 years of age, when fecal impaction reached the splenic flexure, a colostomy was necessary. He was considered to possibly have a megacolon (Hirschsprung's disease).

The colostomy was of the double-barreled type. It brought new problems, although it saved the patient's life. In the first 11 years of his life he had had 11 major operations, the first series having been directed at the anal opening and the subsequent ones at the colostomy problem. Shortly after the first colostomy was established, it prolapsed several inches. This was shortened surgically. Within a few months' time the colostomy then retracted. At operation, the descending colon was fixed to the parietal peritoneum. In August, 1949, a permanent single-barreled colostomy was done. In October, the single-barreled colostomy had stenosed, and this was corrected surgically. In December, 1949, the colostomy again prolapsed and a plastic surgical procedure was done. After this the colostomy gave no further technical troubles.

From the Department of Surgery, Hollywood Presbyterian Hospital–Olmstead Memorial.

The fistulous anal tract meanwhile had persisted in incontinent foul-smelling discharge and soiling. From the human interest point of view it produced quite a family problem. The mother stated that the boy was totally immune to the odors not only from the fistulous drainage but from the colostomy soiling as well. Three teen-aged daughters in the family objected to the odors in their home when they brought in their friends. Beyond all this, the parents could well foresee the ostracism which would be in store for their son as he matured. The family history was negative for any developmental anomalies.

Diagnostic Survey.—Height, weight, and other body measurements and results of studies of the endocrine system were all within normal limits for a male of this age (fig. 1). On physical examination no other anomalies could be found. Results of laboratory studies of urine and blood were within normal limits. X-ray survey, including intravenous pyelograms, of heart, lungs, gallbladder, and gastrointestinal tract showed normal results except for x-rays of the colon. X-rays of the skull were normal. A scout film of the abdomen taken on June 21, 1951, showed a remnant of rectal pouch containing two large scybala, each measuring several centimeters in diameter. After this a catheter was inserted into the fistulous tract and barium introduced. At the same time a barium enema was done through the colostomy stoma. The film (fig. 2) shows the relationship of the rectal pouch and the colon. Except for considerable shortening of the descending colon, the colon appeared quite normal.

This boy had a higher than average I.Q. He did very well in school. He had no discernible conflicts.

Analysis.—After a great deal of thought and study had been applied to this boy's problem it did not appear to be hopeless. The number one problem was whether or not a workable, functioning sphincter ani muscle could be constructed and developed. He had the rectal pouch and the

anal fistulous tract, totally divorced from the single-barreled permanent colostomy. This was fortunate in that it provided an isolated unit of the problem for attack, which would in no manner disturb his health or digestive tract otherwise, while the plan for construction and development of the anal

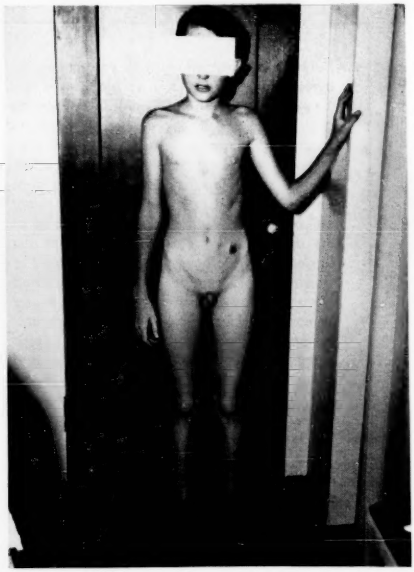


Fig. 1.—Twelve-year-old boy with permanent colostomy and anorectal fistula.

sphincter would be in progress. If a fully functioning sphincter could be provided, then transplanting of the colon to the rectal pouch would be justified. If the sphincter could not be made to perform fully, then the patient would be spared any further ordeal with his colostomy or any further abdominal surgery.

The Plan.—The projected plan was essentially simple. The first procedure would be a plastic reconstruction of the area of the anal plate. When healing had occurred, this would be followed by a regimen of carefully graduated exercises, scheduled, highly disciplined, and over a period of weeks or months. If successful, the results would not be elusive. A sphincter either works or does not work satisfactorily. If a satisfactory sphincter could be developed, then the colon would be brought down and joined with the rectal pouch and the colostomy removed.

While the plan appears simple, there are some basic factors to be considered. Each has an important bearing. Embryologically the internal and external anal sphincters are distinct entities, the external having a myoneural mechanism almost totally voluntary in control. Aside from subsequent aid from the accessory muscles of defecation, the external sphincter would be what we would have to work with. But this boy had never known a sphincter reflex, since he had always been incontinent and at 9 years of age had had the colostomy. The myoneural units of the external sphincter were surely present, even though totally undeveloped. This is readily demonstrable. As an example of undeveloped voluntary muscle, consider the three external ear muscles for moving our ears: Few people can move their ears because these muscles have not been developed. That they can be developed for entertainment purposes is readily recognized. It requires diligent exercise.

The next factor lay in the extensive scar tissue enveloping the anal sinus around which would be distributed the myoneural units of the external sphincter. This scar tissue had been built up over the 11 years from repeated attempts at repair and dilatations and the localized infections that naturally followed. By careful and diligent dissection followed by well-founded plastic surgical principles, there was the possibility of salvaging enough of the myoneural units to reconstruct the sphincter.

Assuming success to this point we come to the commonest problem of imperforate anus, common indeed to any tubal tract, namely, scar tissue contracture and stenosis. This I was prepared to deal with from past partly related experiences.[3] If the new anal opening was packed in wide dilatation, with use of a vented pack and not less than 4 cm. in diameter, the new scar tissue would be laid down in this radius within the first 24 hours. Now, if the pack were to be left in for four or five days it would fall out of its own accord, leaving a widely dilated anal opening. After healing was satisfactory, the muscle exercises, if successful, would bring the opening down to zero, since the muscle pattern is such as to close the opening; and the scar tissue, having been cast in wide dilatation, would have to follow, not lead. A technical point here is that no raw surface be permitted in the anal opening to give rise to pain and later scar tissue. With absolute hemostasis and administration of antibiotics a primary healing could be anticipated.

Fig. 2.—Roentgenogram showing rectal pouch and short descending colon ending in permanent colostomy.

If the surgical aspect of the sphincter problem went well, the next step would be the regimen of exercises, planned and graduated over a period of months if necessary. For the voluntary exercises of a muscle a counterpressure is necessary. For this purpose I planned to use the Kegel perineometer, for a number of reasons. The new anal orifice would

be large to start with, and the compression cylinder of the perineometer is also large, having been designed for vaginal purposes. Additionally, the perineometer has a gauge which would indicate progress from day to day. If the patient succeeded with the perineometer, the next step would be a colon tube with graduated water pressure being increased

Fig. 3.—New anal opening healed in wide dilatation, before exercise regimen was begun.

as the boy made progress. If the progress with the colon tube were satisfactory, then the same routine with a catheter would be followed. Finally, if the plan were to be effective, the patient would have to be able to hold fluid in the rectal pouch for prolonged periods of time while he went about his daily routine at home and at school. If this last accomplishment could be obtained to the absolute satisfaction of the boy, his parents, and the surgeon, then the restoration of the bowel continuity would be warranted.

This discussion and plan was presented to the boy and his parents. The parents readily accepted it. The boy wanted none of it since it meant at least one more operation and, if successful, still another operation. But he agreed to it. On July 23, 1951, I did the plastic reconstruction of the anal opening.

Surgical Procedure.—Under intratracheal anesthesia, the patient was placed in reverse Trendelenburg position on the table with the buttocks widely retracted by adhesive bands secured to the table. Beginning with the lubricated little finger, slow steady pressure was applied until the finger was fully beyond the stricture. Next the same procedure was carried out with use of the index finger and then the thumb; then the index finger of one hand and the little finger of the other hand were applied simultaneously until it was possible to insert a speculum into the opening. When the retractor was in place, the next procedure was directed at removal of the two large scybala which were known to be in the rectal pouch. It was possible to grasp the first fecal mass with a placenta forceps which served to steady the scybalum for further manipulation within the rectal pouch, since it was much too large to deliver through the opening. Thus steadied, the mass, which was very tough in consistency, was gradually divided and removed by morcellation. The same procedure was applied for the removal of the second large fecal mass, after which the rectal pouch was irrigated with sterile saline solution.

At this time careful examination of the nature of the stricture demonstrated that the anorectal mucosa came up to the inner border of the stricture in a reasonably sharp margin radially and had withstood the dilatation of the stricture without being torn. There was an extremely dense transverse scar tissue band on the border of the anus anteriorly. This appeared to present the greatest mechanical factor involved in the stricture. At this point I divided this band in the middle by an incision transverse to the band but in the longitudinal body axis. It then became apparent that dilatation was readily accomplished. This incision was extended inwardly down on to the normal mucosa and outwardly down to normal skin. With a slow tedious sharp dissection, with use of small instruments, the scar tissue was now dissected back from the center to normal skin externally. Most of the scar tissue appeared to be in the skin itself without too much invasion of the subcutaneous tissues. Dissection was carried inward to the mucosa where the scarring was minimal. In only a few points was it necessary to elevate the mucosa in order to eradicate the scar tissue.

The dissection having been completed, the anal opening was widely open. In order to gain the maximum mechanical advantage in the size of the opening, I now sutured the wound transversely to its original axis, using interrupted 000 chromic catgut suture on intestinal needles. The mucosa was likewise sutured to the skin margin with interrupted 000 atraumatic catgut suture, in those places where it had been elevated. This having been completed, it was possible to admit three fingers into the new anal opening. There were no denuded areas, and there was mucosa to skin apposition at all points. After this a large-gauge gum rubber tube was tightly wrapped with 4-in. gauze and impregnated with tetracaine (Pontocaine) hydrochloride ointment, until the diameter of the pack was approximately 4 cm. This was placed in the anorectal opening without any difficulty and secured firmly with dressings and tape. The patient lost very little blood during the operation. Postoperatively he received

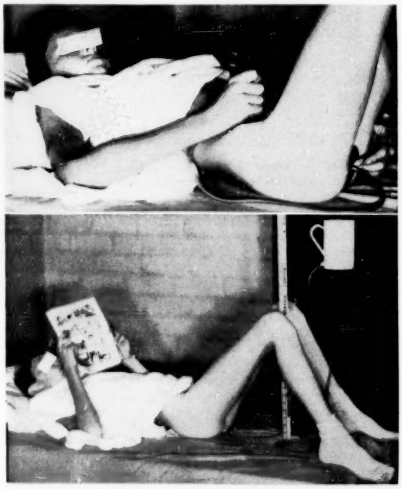


Fig. 4.—*Above*, first series of exercises begun with perineometer. *Below*, hydraulic phase of exercises with use of colon tube and enema can for pressure.

antibiotics. The pack came away on the fifth postoperative day. Healing was primary. Figure 3 shows the anal opening, widely dilated, after healing.

On July 31, 1951, the boy and his mother were instructed on the use of the perineometer in conjunction with a demonstration (fig. 4, *above*). It was necessary to impress on the boy that this was his project, that he would have to keep a daily log of all dates, readings attained, and time spent in

exercises, and that he would have to bring this record to the office each time for inspection. This was necessary since he was prone to delegate all problems to his mother. The exercises with the perineometer consisted of 15 minutes of voluntary contractions on the pneumatic cylinder, performed

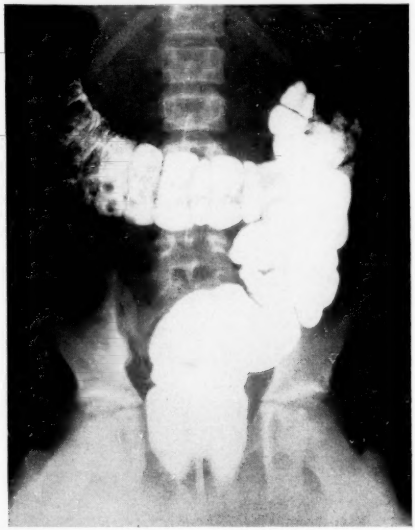


Fig. 5.—Roentgenogram of colon 10 months after restoration of intestinal continuity.

three times each day while lying supine, and recording each time the height to which the gauge rose. His log records were extremely meticulous and neat.

By Aug. 31, 31 days after the start of the exercises, his progress was so successful that he had exceeded the capacity of the perineometer. A satisfactory sphincteric contraction could be felt over the index finger. At this time the plan advanced to the hydraulic phase as scheduled. A colon tube was inserted into the anal opening, an enema can attached, and a yardstick used for a gauge (fig. 4, *below*). Again the program was for three 15-minute periods of exercise per day, being carried out in the bathtub at the start. By arrangement he was permitted to raise the can 2 in. if he had been successful in holding it without leakage in the previous exercise period. He was to continue his log. By Oct. 17, 1951, he had exceeded the yardstick elevation by an estimated 2 ft., for pressure. His sphincter contraction on the index finger was good. The colon tube was replaced with a catheter and the same exercise-pressure program carried out.

By Nov. 13, 1951, he could fill the rectal pouch under pressure, remove the catheter, play football for two hours, have no soiling, and then electively go to the toilet and expel it. The anal opening readily admitted the index finger without pain. He had positive satisfactory sphincteric control, in my opinion. I advised the parents that I was prepared to proceed with the abdominal phase of the plan but would prefer that they first have the boy checked by another surgeon of their choice in order to evaluate any enthusiasm which might seem warranted. This was immediately done by an officer of the U. S. Maritime Hospital. He concurred in the satisfactory status of the anal sphincter.

On Dec. 8, 1951, I did the abdominal phase of the plan. A detailed outline of the proposed surgery had been prepared for all assistants and nurses. Plan A called for the simplest procedure one could hope for, that is, mobilization of the descending colon and anastomosis of it to the rectal pouch. In view of the previous shortening and ventral fixation of the intestinal segment, plan A might not be workable. Under plan B I proposed to mobilize the splenic flexure in order to gain adequate length. Ordinarily this would not have appeared too formidable, but in view of the many previous operations and the shortening and ventral fixation, this plan might also not be feasible. Under plan C an alternative appeared, which had been noted in an upright film of the colon. This is not apparent in figure 2 because it is a prone film. The patient had an extensive ptosis of the transverse colon, and under plan C, if necessary, I planned to bring down the distal end of the transverse colon for the anastomosis.

After the abdomen was opened and the conditions estimated, they were found to be better than expected. It was possible to mobilize enough descending colon from above and enough rectal pouch from below to do an end-to-pouch anastomosis without any tension. The colostomy was removed. An appendectomy was done.

Postoperative convalescence was uneventful. On the third postoperative day the patient went to the toilet and had a bowel movement—fully controlled. He surprised us with his lack of enthusiasm over this event. On the morning of the fourth postoperative day he was in a state of great elation. He had been to the toilet and had sat for 30 minutes before allowing his bowels to move. His explanation for this happi-

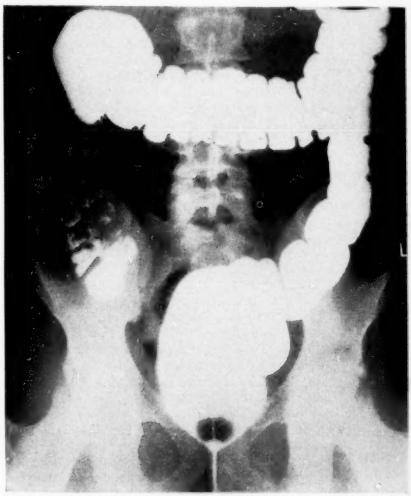


Fig. 6.—Roentgenogram of colon six and one-half years after restoration of intestinal continuity.

ness on this morning was that "It was the first time that I thought it would work." He left the hospital on the eighth postoperative day.

Results.—The patient returned to school after the Christmas holidays without loss of time. Contrary to plan he indulged himself in all of the varieties of the hamburger and

Coke diet, but without ill-effects. He has participated in athletics through high school and three years of college. He has never had any dietary restrictions. He has never had any dilatations of the anal opening nor need for them. His bowels move normally without any laxatives. He controls gas successfully. He can carry out the 2 oz. of castor oil regimen and drive 25 miles for a barium enema study. The first postoperative barium enema was done Oct. 11, 1952 (fig. 5). The last and only other study was done June 30, 1958 (fig. 6). The anal opening readily admits the index finger without pain. A fully satisfactory sphincteric contraction over the finger is readily demonstrated. The patient is now 6 ft. 5½ in. (197 cm.) tall and very successful in his third year of college.

Summary

A planned procedure for the problem, fortunately not common, of a young person with a colostomy and anal incontinence was carried out. It represented the combined application of sound plastic surgical principles, rehabilitation procedure for the development of the latent sphincter ani muscle, and restoration of bowel continuity and abolition of the colostomy. The theory advanced for the reconstruction of the anal sphincter in wide dilatation to avoid contractures, together with the subsequent muscle development program, may be a new approach. That it has been fully successful is encouraging. The principles can be applied in other procedures. It will be noted that this report has been delayed for seven years. This has been so elected in order that the boy reach maturity, that enough time elapse to permit proper evaluation of the results without undue enthusiasm.

1527 Wilshire Blvd. (17).

References

1. Duffy, J. J.: Imperforate Anus and Rectourethral Fistula in 27-Year-Old Man: Report of Case, J. A. M. A. **145**:545-548 (Feb. 24) 1951.

2. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941.

3. Duffy, J. J.: Anal Sphincters: Their Preservation, Reconstruction, and Regeneration, Annals of Ninth International College of Surgeons, São Paulo, Brazil, April 26 to May 2, 1954, vol. 3, pp. 617-626.

BLEEDING TENDENCY IN UREMIA

Joseph A. O'Grady, M.D., Jackson, Miss.

That uremia is associated with bleeding has been known since the turn of the century.[1] Mason [2] has reported that bleeding from the mucous membranes of the gastrointestinal tract occurs in 21.1% of the cases. Despite this knowledge, however, the mechanism of such bleeding is not known. Recently there have appeared in the literature several articles [3] which deal with this aspect of this perplexing problem. These articles have been inconclusive in their results. In few of them have serial determinations been done on a series of patients.

Since patients in a Veterans Administration hospital tend to be rehospitalized in the same hospital, it was decided to check the coagulation mechanism on any patient with a blood urea nitrogen level of more than 30 mg. per 100 ml., expecting that in this way more than one determination would be done on an individual patient as the uremic process progressed. By this method of selection, single coagulograms [4] were done on 42 patients with blood urea nitrogen levels ranging from 24 to

From the Research Laboratory, Veterans Administration Hospital, and the Department of Medicine, University of Mississippi Medical School.

Clues as to the reason for hemorrhagic phenomena among uremic patients were sought in a study of 65 men whose blood urea nitrogen levels were either above 24 mg. per 100 ml. or fluctuating about uremic levels. In 49 of the patients the blood urea nitrogen level was over 50 mg. per 100 ml. A series of tests was done, including the clotting time in glass, clotting time in silicone-treated glassware, one-stage prothrombin time, prothrombin consumption, platelet count, and, in some cases, thromboplastin generation, clot retraction, and capillary fragility. No impairment of clot retraction could be demonstrated in any of the patients, and no single test gave consistently abnormal results in these patients. There was, however, a rough correlation in that more of the tests gave abnormal results at the higher levels of uremia.

186 mg. per 100 ml. and multiple coagulograms were done on 23 patients whose blood urea nitrogen levels were changing. This change was usually a progressive increase of the blood urea nitrogen level, although in some patients the level fluctuated and in others it showed a decline. The diseases represented in the multiple determinations are given in table 1.

Methods

A series of tests (coagulogram)[5] was done, consisting of clotting time in glass, clotting time in glassware treated with an organosilicate compound (Desicote), one-stage prothrombin time, prothrombin consumption, and platelet count. In selected cases, thromboplastin generation and capillary fragility tests were done.

The clotting time was done in three 75-by-8-mm. glass tubes at room temperature, the time of clotting in the third tube being taken as the clotting time. The same method was used in determining the clotting time in siliconized, treated glassware. Times up to 15 minutes were considered normal in glass, and times up to 35 minutes were considered normal in siliconized glassware.

TABLE 1.—*Disease Entities in Patients Given Multiple Coagulograms*

Disease	No. of Patients	No. with Clinical Bleeding
Arteriolar nephrosclerosis	6	2
Chronic pyelonephritis	3	0
Chronic glomerulonephritis	3	2
Chronic renal disease and cirrhosis of liver	2	1
Hydronephrosis and pyelonephritis	1	0
Adenocarcinoma of pancreas with acute pancreatitis and lower nephron nephrosis	1	0
Intercapillary glomerulosclerosis (Wilson-Kimmelstiel syndrome)	1	1
Diffuse hemorrhagic pericarditis of unknown etiology	1	1
Hemorrhage, shock, and oliguria after prostatectomy	2	2*
Nephrosclerosis and cortical necrosis	1	0

*Fibrinolysin found not to be a factor.

Prothrombin consumption was determined according to the method of Sussman and associates.[5] Commercially prepared fibrinogen was used. A time of less than 25 seconds was considered abnormal.

The one-stage prothrombin time was determined according to the method of Quick,[6] with use of thromboplastin prepared from human brain during the early part of the study and, later, commercially prepared rabbit brain. A control was recorded with each determination and the patient's value checked against it. The thromboplastin was prepared to give a normal value in the 14-to-15-second range.

The platelet count was done with a counting chamber, with use of both sides of the chamber and a calibrated red blood cell pipet. The diluting fluid used was a 1% solution of edathamil disodium (Sequestrene), colored with a few crystals of cresyl blue. Normal values were between 200,000 and 400,000 per cubic millimeter. The specimens were collected from siliconized glassware, and the value obtained by the direct count was checked against a coverslip preparation made from the same specimen and stained with Wright's stain.

The prothrombin consumption index was obtained by dividing the observed one-stage prothrombin time by the observed prothrombin consumption time. Since the same batch of thromboplastin was used in both determinations, variations due to the thromboplastin should be equalized. The normal range obtained on patients without known coagulation defects or bleeding tendencies was found to be 30-55%. This index was based on a formula devised by Merskey.[7] Abnormal consumption is denoted by values greater than 55%.

The thromboplastin generation test was done according to the method of Biggs and Douglas,[8] as modified by Bell and Alton.[9] Clot retraction was done according to the method of Budtz-Olsen.[10] No impairment in clot retraction could be demonstrated in any of the patients. These results are not quoted below. In no instance was any evidence of dissolution of the clot observed.

One hundred two coagulograms were done on 65 patients, 23 of whom had more than one coagulogram done during the course of illness. Of this latter group, 17 died. The thromboplastin generation test was done on 19 occasions on 15 patients, and results were always within normal limits, as judged by a concomitant examination on a normal control subject. Forty-nine of the coagulograms were done on patients having a blood urea nitrogen level of more than 30 mg. per 100 ml.

Results

The incidence of abnormalities occurring at the different ranges of blood urea nitrogen level is summarized in table 2. Table 3 shows the changes in the various tests of the coagulogram in relation to the change in the blood urea nitrogen level in the 23 patients who had more than one coagulogram. In addition to the patients included in these tables, two patients were studied who showed increasing abnormalities as the blood urea nitrogen level increased and then returned to normal as it decreased.

Since no constant defect in the coagulogram was demonstrated as the blood urea nitrogen level increased, it was decided to analyze the results according to the number of coagulation defects found at different ranges of the blood urea nitrogen level. The results are presented in table 4.

Comment

In table 2 are presented the results of the various tests in the coagulogram in all the patients with uremia included in this study. The percent-

ages of abnormal results seem quite high in the lower levels of blood area nitrogen, and this is particularly true of the prothrombin times. However, an analysis of the degree of abnormality reveals that of the 12 abnormal prothrombin times at a time when his blood urea nitrogen level was 120 mg. per 100 ml. and again when it was 140 mg., although he was oozing blood from his mucous membranes on both occasions and the tourniquet test finding was only 2+.

TABLE 2.—*Incidence of Abnormal Findings in Each Test of Coagulogram*

Range of Blood Urea Nitrogen Level, Mg. %	Coagulograms, No.	Abnormal Findings: One-Stage Prothrombin Time No.	%	Prothrombin Consumption No.	%	Clotting Time: Glass No.	%	Clotting Time: Siliconized No.	%	Platelet Count No.	%	Prothrombin Consumption Index No.	%
24- 50	40	19	47.5	3	7.5	0	0	1	2.5	8	20.0	12	30.0
51- 75	23	13	56.5	8	34.8	0	0	1	4.3	6	26.1	15	65.2
76-100	22	11	50.0	6	27.3	1	4.5	5	22.7	5	22.7	11	50.0
100+*	17	12	70.6	10	58.8	1	5.9	3	17.6	13	76.5	10	**58.8**
Total†	102	55	53.9	27	26.4	2	2.0	10	9.8	32	31.4	47	**47.1**

*Highest level, 186 mg. %.
†Totals show which tests were most frequently abnormal in patients with uremia.

encountered in patients having a blood urea nitrogen level of more than 100 mg. per 100 ml., a group in whom it would be expected that such an abnormality would be significant, the range of difference between the patients and their controls was 1.4 to 8.5 seconds, with an average of 3.3 seconds. It is doubtful that such minor prolongation of the prothrombin time would be directly responsible for the clinical bleeding observed. Moreover, some of the patients studied had evidence of liver disease which was not related to or associated with the uremic process.

From tables 2 and 3 it appears that the coagulation measurements most affected by an increasing blood urea nitrogen level are the one-stage prothrombin time, the platelet count, the prothrombin consumption, and the prothrombin consumption index. These tables reveal that the coagulation impairment is directly related to the height of the blood urea nitrogen level.

It has been claimed that the bleeding tendency in uremia is due to increased fragility of the capillaries.[3d] During the course of this study, several tourniquet tests were done and in none of them was there a greater response than 15 to 20 petechiae per circle of 2.5-cm. diameter. In one patient no coagulation defect could be demonstrated at a time when his blood urea nitrogen level was 120 mg. per 100 ml. and again when it was 140 mg., although he was oozing blood from his mucous membranes on both occasions and the tourniquet test finding was only 2+.

TABLE 3.—*Changes in Individual Coagulograms in Twenty-three Patients with Uremia, as Correlated with Changes in Blood Urea Nitrogen Level*

	Progressive Abnormality: Rising Level, No.	Progressive Abnormality: Declining Level, No.	Progressive Improvement: Rising Level, No.	Progressive Improvement: Declining Level, No.	Results Unchanged with Changing Level, No.
Prothrombin time	9	1	2	2	10
Prothrombin consumption	8	0	1	0	14
Platelet count	9	0	2	0	12
Prothrombin consumption index	14	2	2	3	2
Clotting time, glass	1	1	0	1	20
Clotting time, siliconized	5	0	1	0	17

Other investigators in the field have felt that the platelets are at fault.[11] Larrain and Adelson[3a] and Larrain and Langdell[3b] felt that an inhibitory substance might be present. In all these investigations the platelet levels have been found to be low in some of the patients, but in few of them have they been low enough to be felt responsible for the clinical evidence of bleeding. These same investigators[12] have also found that in some of their patients there is a shortening of the prothrombin consumption time,[12] prolongation of the clotting time in siliconized glassware,[13] and abnormal thromboplastin generation.[3c] Lewis and co-workers[3c] found reduced thromboplastic function of the platelets in 8 patients, reduced accelerator activity in 7, and both in 4 of 12 patients studied.

My results are much in accord with these investigations with one important exception, namely, that the thromboplastin generation results were all within normal limits. Of the 19 such examinations performed, 6 were found to be in patients with abnormal prothrombin consumption and prothrombin consumption index yet having platelet counts in excess of 150,000 per cubic millimeter. It is most unlikely that the prothrombin consumption shortening and the prothrombin consumption index increase can be assumed to be on a basis of low platelet counts in these persons. In the method used,[9] a brain extract is substituted for the patient's platelets. This extract does not have thromboplastic activity but is capable of normalizing the thrombo-

TABLE 4.—*Total Incidence of Abnormal Coagulograms, Correlated with Blood Urea Nitrogen Levels*

Range of Blood Urea Nitrogen Level, Mg. %	Total No. of Tests	Abnormal Results: No.	%
24- 50	240	43	17.9
51- 75	138	39	28.3
76-100	132	39	29.5
100+	102	49	48.9

plastin generation test in platelet-deficient plasma. Therefore, this finding would seem to indicate that the platelets not only are quantitatively abnormal in some instances of bleeding but also may be qualitatively abnormal, as suggested by Rath and associates.[3e]

Whatever the underlying mechanism is, it is evident that, as the uremic process progresses, the number of coagulation abnormalities increases. Whether this is due to a deterioration of one of the factors which results in defects in the others measured, or whether the bleeding tendency is due to multiple coagulation deficiencies occurring separately as a result of the generalized deterioration of the patient, cannot be stated from this study. The normal clotting time (siliconized glassware) in most of these patients would make the possibility of a circulating anticoagulant unlikely. Also, the fact that the thromboplastin generation findings were normal would seem to argue against the presence of an inhibitor unless it had a specific effect on the platelets themselves. It does seem from the study that, if the bleeding is due to one factor, it is probably due to the defective formation of thromboplastin on a basis of a qualitative defect in the platelets.

Summary

A series of tests, including clotting time, one-stage prothrombin time, prothrombin consumption, platelet count, and, in selected cases, thromboplastin generation and the Rumpel-Leede test were done on 65 males whose blood urea nitrogen levels were elevated. Twenty-three of these patients had multiple tests as the blood urea nitrogen level was changing; most of them were tested as it was increasing. It was found that there was a rough correlation between the number of abnormal results and the height of the blood urea nitrogen level, with more of the tests giving abnormal results at the higher levels. While no single test finding tended to be consistently abnormal, the platelet count, the prothrombin consumption, and the prothrombin consumption index seemed to be most regularly affected. The bleeding tendency in uremia may be due to a qualitative defect in the platelets.

Nichols Medical Group, Houston at Eighth Streets, Plainview, Texas.

Mrs. Myra Lowery supplied technical assistance in this study.

References

1. Riesman, D.: Hemorrhages in Course of Bright's Disease with Especial Reference to Occurrence of Hemorrhagic Diathesis of Nephritic Origin, Am. J. M. Sc. **134**:709-716, 1907.

2. Mason, E. E.: Gastrointestinal Lesions Occurring in Uremia, Ann. Int. Med. **37**:96-105 (July) 1952.

3. (*a*)Larrain, C., and Adelson, E.: Hemostatic Defect of Uremia: I. Clinical Investigation of Three Patients with Acute Post-traumatic Renal Insufficiency, Blood **11**:1059-1066 (Dec.) 1956. (*b*) Larrain, C., and Langdell, R. D.: Hemostatic Defect of Uremia: II. Investigation of Dogs with Experimentally Produced Acute Urinary Retention, ibid. **11**:1067-1072 (Dec.) 1956. (*c*) Lewis, J. H.; Zucker, M. B.; and Ferguson, J. H.: Bleeding Tendency in Uremia, ibid. **11**:1073-1076 (Dec.) 1956. (*d*) Kuhlback, B.: Bleeding Tendency in Chronic Renal Failure, Acta med. scandinav. **157**:173-177, 1957. (*e*) Rath, C. E.; Mailliard, J. A.; and Schreiner, G. E.: Bleeding Tendency in Uremia, New England J. Med. **257**:808-811 (Oct. 24) 1957.

4. Bell, Warren N.: Symposium on Clinical Medicine: Clinical Use of Coagulogram, M. Clin. North America **37**:1843-1853 (Nov.) 1953.

5. Sussman, L. N.; Cohen, I. B.; and Gittler, R.: Clinical Application of Simplified Serum Prothrombin Consumption Test, J. A. M. A. **156**:702-705 (Oct. 16) 1954.

6. Quick, A. J.: Physiology and Pathology of Hemostasis, Philadelphia, Lea & Febiger, 1951.

7. Merskey, C.: Consumption of Prothrombin During Coagulation: Defect in Haemophilia and Thrombocytopenic Purpura, J. Clin. Path. **3**:130-141 (May) 1950.

8. Biggs, R., and Douglas, A. S.: Thromboplastin Generation Test, J. Clin. Path. **6**:23-29 (Feb.) 1953.

9. Bell, W. N., and Alton, H. G.: Brain Extract as Substitute for Platelet Suspensions in Thromboplastin Generation Test, Nature, London **174**:880-881 (Nov. 6) 1954.

10. Budtz-Olsen, O. E.: Clot Retraction, Oxford, England, Blackwell Scientific Publications, 1951.

11. Reference 3*c* and *e*.

12. Reference 3*a*, *b*, *c*, and *e*.

13. Reference 3*a* and *b*.

INFECTION AND DIABETES.—Even a mild infection may considerably increase the severity of the diabetes and require much more insulin than is usually given. When the infection is severe, as in carbuncles, appendicitis with peritonitis, or empyema of the gallbladder, the diabetic patient may be easily pushed into acidosis or coma. Greatly increasing the amount of insulin may or may not control the acidosis or the coma, and in order to restore the patient to his pre-acidotic condition it may be necessary to operate upon him and rid him of the infection. In such an emergency, one would have to operate in the presence of uncontrolled diabetes and then try to control the acidosis in the postoperative period. Attention should also be called to the fact that, once the patient is free of the infection, his insulin requirements may rapidly diminish. The physician must be on guard for this probability in order to avoid producing insulin shock.—D. H. Wagner, M.D., The Preparation and Care of Diabetic Patients Requiring Surgery, *The Surgical Clinics of North America*, February, 1959.

SAFFLOWER OIL–PYRIDOXINE AND CORN OIL–PYRIDOXINE EMULSIONS

THEIR EFFECT ON SERUM CHOLESTEROL LEVELS IN YOUNG ADULT MALES WHEN USED AS SUPPLEMENTS TO A NORMAL DIET

Richard Perkins, M.D., Irving S. Wright, M.D.
and
Barbara W. Gatje, B.S., New York

The effects of using safflower oil and corn oil as supplements to the usual diet were studied in 22 young healthy men. Serum was obtained weekly from each subject by venipuncture, to be analyzed for total cholesterol. Determinations during an initial observation period of five weeks afforded a basis for dividing the subjects into two matched groups with equal mean serum cholesterol levels (221 mg. per 100 cc.). One group thereupon received a supplement of safflower oil for seven weeks followed by corn oil for seven weeks; the other group received corn oil for seven weeks followed by safflower oil for seven weeks. In both groups a consistent decline in the mean cholesterol levels was observed as the experiment progressed, but the changes were not convincing because of the wide individual variations and no differences between safflower and corn oil were revealed under the conditions of this experiment. Significant cholesterol-lowering effect of these two oils can be demonstrated only if they are used as replacements for, rather than additions to, some of the saturated fats in the usual diet.

When unsaturated vegetable oils are substituted for saturated animal fat in the human diet, sustained reductions in levels of serum lipids can usually be achieved.[1] It was therefore to be hoped that vegetable oils could be used as supplements to the regular diet, so that reductions in levels of total serum cholesterol and other lipids might be possible without the restrictions of a low-fat diet. Several vegetable oil emulsions have been marketed recently and have been widely used in the treatment of patients with hypercholesteremia and arteriosclerosis.

Safflower oil and corn oil are the two oils most commonly used at present. Several of the emulsions of these oils now available also contain pyridoxine, which may be involved in fat metabolism.

An earlier report [2] from this laboratory described an experiment in which a safflower oil emulsion (without pyridoxine) was administered, with placebo controls, as supplements to young male volunteers who were maintained on an otherwise normal diet. Figure 1 is reproduced to show the results of that study, in which essentially the same group of volunteers participated as were used in the present study. No demonstrable depressant effect on total serum cholesterol levels was observed, although the volunteers took 50 Gm. of the oil daily for seven weeks.

The present experiment was designed to test the effects on the serum cholesterol level in 22 young male subjects of a safflower oil emulsion with pyridoxine and of a corn oil emulsion with pyridoxine, each used as a supplement to the usual diet.

Materials and Methods

Selection of Subjects.—Twenty-two young male medical students, averaging 24 years of age (range 22 to 26) were selected to serve as paid volunteers. All but one of these had served as volunteers in the previous experiment. None had a history or clinical evidence of atherosclerosis or thyroid disease.

Control of Diet.—Questionnaires were used to establish the following average composition of the diet: total calories, 2,400 (range 1,900 to 3,100); calories derived from fat, 40% (range 32 to 45%); and total daily fat intake, 102 Gm. (range 86 to 116 Gm.). The subjects were asked to adhere as closely as possible to their usual diets throughout the experiment but were allowed to omit desserts if they found themselves gaining weight. Each subject was weighed weekly.

Experimental Design and Method.—Serum was obtained weekly by venipuncture, with the subject in the fasting state, and analyzed for total serum cholesterol level by a modification of the method of Bloor. Most determinations were made with fresh serum, although some were performed with serum which had been frozen for several days at –15 C.

There was a preliminary control period of five weeks, during which time the subjects followed their usual activities and diets. At the end of this period, the 22 subjects were matched according to nearest average serum cholesterol levels observed

From the Vascular Section, Department of Medicine, New York Hospital–Cornell University Medical College.

that far in the experiment. Half of the volunteers were then given a safflower oil emulsion supplement and half a corn oil emulsion supplement. Because the two preparations available differed in their water content, 150 cc. daily of safflower oil and

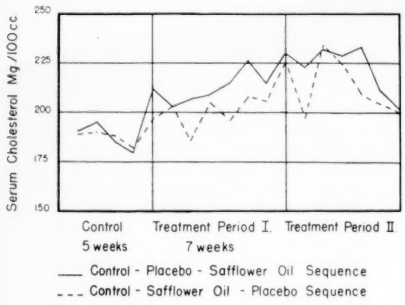


Fig. 1.—Mean total serum cholesterol levels in two groups of 12 subjects each.

90 cc. daily of corn oil were prescribed. However, these dosages both contained an equal amount by weight of the particular oil, approximately 45 Gm. daily.

The safflower oil emulsion contained linoleic acid (as safflower oil), mixed tocopherols, glycerine, emulsifying agents, polysorbate 60, sorbitan trioleate, artificial sweetener calcium cyclamate, artificial flavoring, 0.1% sodium benzoate, and 0.004% propyl gallate plus pyridoxine hydrochloride. The daily dose used contained 45 Gm. of safflower oil and 50 mg. of pyridoxine hydrochloride. The corn oil emulsion contained corn oil, polyoxyethylene sorbitan monostearate and fatty acid monostearate and fatty acid monoglyceride and diglyceride as emulsifiers, natural and artificial flavors, coloring material, 0.005% propyl gallate, and 0.1% sodium benzoate plus pyridoxine hydrochloride. The daily dose used contained 45 Gm. of corn oil and 20 mg. of pyridoxine hydrochloride.

After seven weeks of therapy, the two experimental groups were reversed, so that those who had

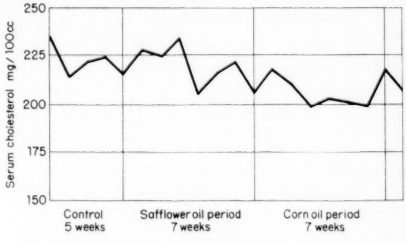


Fig. 2.—Mean total serum cholesterol levels in 11 subjects: control, safflower oil, corn oil treatment sequence.

taken safflower oil then took corn oil and those who had taken corn oil then took safflower oil. After a total of 14 weeks of therapy, use of the vegetable oil supplements was discontinued and one final cholesterol level determination was performed after each subject had been without any supplement for a week.

Plasma studies in certain of the volunteers were done serially by means of the thrombelastograph, the results of which will be the subject of a separate report from this laboratory.[3]

TABLE 1.—*Weekly Serum Cholesterol Level Determinations, in Milligrams per 100 Cc., During Control, Safflower Oil, and Corn Oil Treatment Periods*

Case No.	Week No.	Control						Safflower Oil							Corn Oil							
		1	2	3	4	5	Av.	6	7	8	9	10	11	12	Av.	13	14	15	16	17	18	19	Av.	20*
1		...	232	232	202	196	219	252	231	220	188	205	205	159	208	208	202	200	214	188	183	200	199	200
2		198	183	202	208	198	200	205	171	214	168	214	220	196	198	183	198	208	198	202	193	214	201	183
3		303	288	280	311	252	291	297	288	339	247	288	300	267	292	297	300	186	226	232	252	280	248	232
4		214	232	200	220	280	248	236	200	288	247	226	230	232	251	232	232	247	232	230	220	200	237	252
5		138	129	154	168	121	147	208	143	...	133	161	171	163	163	168	147	147	117	143	138	147	144	143
6		280	220	252	247	214	240	193	236	214	173	196	202	205	202	214	214	198	208	214	198	214	209	200
7		226	200	230	243	230	232	252	226	220	220	223	226	191	223	232	214	211	226	193	177	208	209	208
8		303	247	273	252	264	267	256	252	252	273	243	220	226	247	220	247	208	...	...	208	226	223	232
9		223	177	163	188	168	184	183	166	...	159	193	193	173	178	188	177	193	183	198	188	214	192	183
10		273	260	267	226	247	254	226	240	230	247	230	247	252	230	243	226	247	250	252	252	230	235	252
11		202	188	183	196	188	194	220	240	220	208	188	214	198	213	198	198	177	168	168	...	193	177	208
Over-all average		236	214	222	225	213	225	228	224	235	206	216	222	207	219	218	211	199	202	201	199	218	207	207

* Final determination after 1 wk. without any supplement.

Results

As had been the case in our previously reported study,[2] there was a considerable variation from week to week in the cholesterol levels of the individual subjects. The over-all average, however, during five weeks without therapy was 221 mg. per 100 cc. (range 125 to 311 mg.).

The addition of 150 cc. of safflower oil emulsion with pyridoxine (containing 45 Gm. of oil) to the daily diet of 11 of the subjects was followed by a slight decrease in the average serum cholesterol level (fig. 2). When, after seven weeks of this, 90 cc. of a corn oil–pyridoxine emulsion (again containing

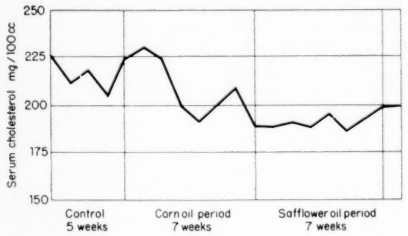


Fig. 3.—Mean total serum cholesterol levels in 11 subjects: control, corn oil, safflower oil treatment sequence.

45 Gm. daily of vegetable oil) was substituted, there continued to be a gradual downward trend in the average cholesterol level (table 1).

In the other group of 11 subjects, with whom the sequence of therapy was reversed, similar results were obtained, i. e., a slight, gradual decrease in the average serum cholesterol level (fig. 3, table 2). In each group the corn oil–pyridoxine emulsion appeared to be slightly more effective.

However, the decrease in average serum cholesterol level during therapy was at no time statistically significant, whether any single week or the entire seven-week treatment period was taken as an example. That is, the decrease in average serum cholesterol level at no time was more than twice the standard deviation from the mean established during the control period.

There was very little weight gain noted in these subjects. The average weight gain after 14 weeks' therapy with both vegetable oil emulsions was 0.6 kg. (1.3 lb.). In general, the oil emulsions were tolerated well, despite the large doses used. Occasional episodes of loose stools were reported.

Comment

Rivin and associates [4] have recently emphasized the fact that there may be a considerable biological fluctuation from time to time in total serum cholesterol levels of patients; they pointed out that caution is necessary in drawing inferences from a single cholesterol level determination. The results of the present study, in which wide fluctuations from week to week were observed in individual subjects' cholesterol levels (during both control and treatment periods) reinforce this view.

There is little doubt, however, from the reports of other experimenters, that the use of either corn oil or safflower oil, substituted for most of the fat in the diet, will produce a significant decrease in serum cholesterol levels. But, in this study, the results of the use of these oils as supplements to a regular diet were not significant enough to justify this as a therapeutic procedure.

Similar studies were made on a small group of patients with elevated serum cholesterol levels (more than 300 mg. per 100 cc.). These results will not be reported here in detail, but they resemble the results obtained in the young male volunteers. That is, no significant decrease in serum cholesterol level followed the use of vegetable oil supplements when the diet contained moderately high amounts of saturated fat. But, when a strict low-fat diet was used, the addition of corn oil or safflower oil supplements usually produced a greater decrease in the serum cholesterol level than had the low-fat diet alone.

TABLE 2.—*Weekly Serum Cholesterol Level Determinations, in Milligrams per 100 Cc., During Control, Corn Oil, and Safflower Oil Treatment Periods*

Case No.	Control						Corn Oil								Safflower Oil								
Week No.	1	2	3	4	5	Av.	6	7	8	9	10	11	12	Av.	13	14	15	16	17	18	19	Av.	20*
1	173	183	220	180	232	195	230	229	188	193	183	200	193	204	188	168	168	183	161	173	183	175	177
2	240	230	208	200	240	223	256	220	200	208	229	252	211	227	193	202	200	193	214	193	208	203	208
3	303	288	256	220	273	265	234	202	231	214	214	273	232	229	...	230	229	...	267	252	267	251	247
4	208	183	202	202	202	197	173	175	...	193	202	193	183	187	191	183	177	198	183	202	188	188	163
5	273	264	280	202	243	252	243	198	208	220	...	252	198	217	211	220	217	214	193	230	214	215	198
6	270	247	311	200	252	268	330	252	...	220	223	252	247	244	183	208	226	232	166	193	208	202	252
7	288	186	226	208	226	226	226	223	198	186	168	220	168	203	214	208	191	214	208	208	214	208	...
8	157	163	133	198	191	173	188	172	173	147	161	168	121	161	157	145	150	168	168	138	193	160	168
9	230	247	256	226	208	224	267	240	230	198	214	...	183	224	220	208	220	230	202	198	183	210	226
10	129	125	138	138	125	131	136	125	145	109	141	125	138	131	125	117	116	114	105	102	129	115	154
11	200	208	188	208	247	212	...	231	193	...	220	177	191	198	200	191	177	188	183	214	193	192	193
Over-all average	226	212	218	204	224	217	230	224	198	191	200	209	188	202	188	190	188	194	186	192	198	193	199

* Final determination after 1 wk. without any supplement.

The results of the experiment reported here support the idea that, when a lowered serum cholesterol level is desired, corn oil and safflower oil are best used as supplements to diets markedly reduced in their content of saturated fat. Significant results should not be expected from the use of corn oil or safflower oil, even with the addition of pyridoxine,

as a supplement to the usual American diet. The slight downward trend noted in this study may have been related to the pyridoxine or other ingredients included in the emulsion, since it was not noted with safflower oil alone. Since the effect was, however, not significant statistically, this question is not clearly answered.

Summary

Twenty-two young male subjects were studied during a three-phase experiment lasting 19 weeks. After a five-week control period, they were given, in sequence for seven-week periods, a daily dietary supplement of an emulsion containing pyridoxine hydrochloride and 45 Gm. of either corn oil or safflower oil. The slight decrease observed in average serum cholesterol level was not found to be statistically significant.

This study reemphasizes the fact that, if one wishes to produce a significant lowering of the serum cholesterol level, unsaturated fats should be used only when combined with a diet which sharply limits the use of saturated fats.

525 E. 68th St. (21) (Dr. Wright).

This study was supported by grants from the Lasker, Hampil, Hyde, and Fullerton foundations and from the National Heart Institute.

The safflower oil emulsion used in this study was supplied as Linodoxine by Pfizer Laboratories Division, Chas. Pfizer & Co., Inc., New York. The corn oil emulsion was supplied as Atheroxin by Gray Pharmaceutical Co., Newton, Mass.

Mrs. Lorraine Rose and Miss Ann Florio provided technical assistance in this study.

References

1. Ahrens, E. H., Jr., and others: Influence of Dietary Fats on Serum Lipid Levels in Man, Lancet **1**:943-953 (May 11) 1957. Beveridge, J. M. R.; Connell, W. F.; and Mayer, G. A.: Dietary Factors Affecting Level of Plasma Cholesterol in Humans: Role of Fat, Canad. J. Biochem. & Physiol. **31**:441-455 (May) 1956. Malmros, H., and Wigand, G.: Effect on Serum Cholesterol of Diets Containing Different Fats, Lancet **2**:1-7 (July 6) 1957.

2. Perkins, R.; Wright, I. S.; and Gatje, B. W.: Effect of Safflower Oil Emulsion on Serum Cholesterol Levels in Young Adult Males, J.A.M.A. **166**:2132-2135 (April 26) 1958.

3. Escudero, J., and Wright, I. S.: Value of Thrombelastography in Study of Patients with Thrombophlebitis, to be published.

4. Rivin, A. U.; Yoshino, J.; Shickman, M.; and Schjeide, O. A.: Serum Cholesterol Measurement—Hazards in Clinical Interpretation, J.A.M.A. **166**:2108-2111 (April 26) 1958.

SUBLUXATION OF THE HEAD OF THE RADIUS IN YOUNG CHILDREN

George M. Hart, M.D., Minot, N. D.

Subluxation of the radius at the elbow in children results easily from a combination of pulling and twisting forces. In the seven cases here described the most frequent age was 3 years; the youngest and oldest patients were 10 months and 4 years of age. Three fell while at play, two fell while being held by the arm, one was lifted by the arm, and one had his arm twisted by a playmate. Reduction of the dislocation required but little force and sometimes occurred spontaneously or during examination. The technique for reduction here described involves supination of the forearm while the elbow is held in the extended position and slight pressure is applied to the head of the radius by the physician's thumb. The success of the maneuver is usually attended by a slight clicking sound and immediate relief of pain.

A frequently occurring condition which responds to simple treatment is subluxation of the head of the radius in young children. The injury usually occurs between the ages of 2 and 4 years and is rare after the age of 6. The cause is forcible traction on the extended and pronated forearm and frequently is brought about when the child is lifted by the arm or stumbles while walking when held by the hand, throwing his weight on the arm. After injury there is pain in the region of the elbow, the child refuses to use the arm, and he holds the elbow slightly flexed and the forearm pronated.

The injury was described many years ago and has been known by a variety of names; among these are Malgaigne's luxation, luxation by elongation, nursemaid's elbow, and Gromeyer's injury. Griffin [1] credits Fournier [2] with the first accurate description in 1671. As described by Fournier, the injury caused incomplete dislocation of the head of the radius, relaxation of the ligaments, and downward separation or elongation of the bone. Treat-

From the Section of Orthopaedic Surgery, Northwest Clinic.

ment consisted of supination of the forearm with pressure on the head of the radius followed by flexion of the forearm at the elbow.

Van Arsdale,[3] in a paper read before the surgical section of the New York Academy of Medicine, noted that Hippocrates and Celsus "referred to the matter" and that histories of the subject were given by Malgaigne[4] and Streubel.[5] One hundred consecutive cases were presented in tabular form, giving the age and sex of the child and the nationality of the parents in each instance. He noted that the frequency of the condition was over 1% of surgical injuries in children. Most of his cases were in children 4 years of age or younger. One child was aged 8 years and 6 months. Reduction was accomplished by forced supination and followed by splinting to prevent recurrence.

Stone[6] in 1916 noted that Van Arsdale attributed the injury to the eccentric shape of the radial head, the epiphysis of which became pushed to one side, impinging on the ulna. In an attempt to determine the anatomic explanation of the subluxation, he carried out a number of experiments on 12 arms from material in the anatomic laboratory of the Washington University Medical School. The muscles were removed from these arms, but the ligaments were left intact. When forcible traction was applied to the first arm, the annular ligament could be seen to spring inward, but, on powerful adduction, the external lateral ligament ruptured. In the remaining 11 elbows, subluxation of the radial head was produced in 6. In each of these arms the annular ligament always slipped over the head when the hand was pronated. In the four arms the ligament tore when traction was applied with the hand supinated.

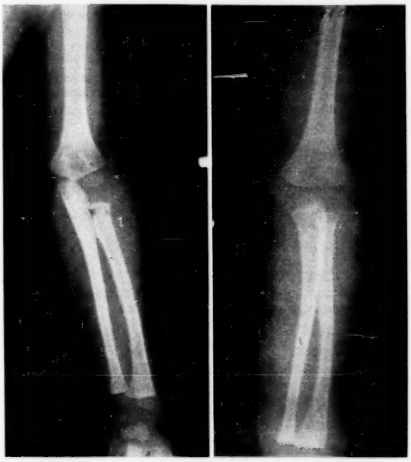
Stone also noted that, whereas standard textbooks on anatomy gave the shape of the radial head as round, measurements of 100 specimens revealed one diameter to be 1.5 mm. greater, on the average, than the other. In some bones the diameter difference was as great as 3 mm. The long diameter was always found to be in the same sagittal plane as the interior portion of the tuberosity of the radius. From these findings Stone explained the reason for subluxation occurring when the forearm was in pronation as follows: "Anteriorly, from the neck of the radius to the head, the rise is an abrupt one. Any traction with the hand supine pulls the ligament against this. Laterally and posteriorly the ascent is quite gradual, so that in pronation the ligament lies over this part and is stretched until it suddenly slips over the head."

Diagnosis

The injury occurs in a child usually between the ages of 2 and 4 years. A history of forcible traction on the extended and pronated forearm is usually described but not always obtained. After injury the child complains of pain in the region of the elbow and holds the elbow slightly flexed with the forearm pronated. The parent notes that the child refuses to use the arm and that attempts to supinate the forearm are painful. Palpation may reveal slight tenderness over the head of the radius, and occasionally the head of the radius may be somewhat more prominent than on the opposite side. Extension and flexion of the elbow are normal. Results of roentgenologic examination are usually negative, but occasionally slight separation between the head of the radius and the capitellum may be visible (see figure).

Treatment

Treatment of subluxation of the head of the radius in children is simple. The subluxation is easily reduced by manipulation as follows: The affected elbow is grasped with one hand with the thumb on the head of the radius. The forearm is held with the opposite hand at the wrist and extended. The forearm is then forcibly supinated, and at the same time slight pressure is made on the head and neck of the radius with the thumb. Upward pressure may be made on the forearm along the shaft of the radius compressing it against the capitellum of the humerus. As supination is carried out a slight click is often felt over the head of the radius, and pain and limitation of supination are relieved. Reduction is usually so easy that it may occur spontaneously or be accomplished by the parent or x-ray



***Left*, slight widening of joint space between proximal radius and capitellum of humerus, with elongation of radius at wrist. *Right*, normal forearm.**

technician during manipulation of the arm. After reduction it is advisable to place the arm in a sling for a few days. The parents should be warned to avoid traction on the child's forearm for several weeks.

Report of Cases

Case 1.—A 10-month-old child fell while being held by the right arm by his mother on Oct. 15, 1951. The child immediately began to cry and refused to use the arm. Examination revealed normal extension and flexion of the arm at the elbow. Supination of the forearm was limited, with pain on forcing. As supination was carried out, a mild click was palpated over the head of the radius and pain was relieved. An x-ray of the elbow was made and was normal. A long arm plaster splint holding the elbow at 90 degrees was applied and remained for four days.

Case 2.—A 3-year-old boy was seen April 7, 1952, complaining of pain in the right wrist. Two days previously, while playing, his sister had rolled on his right arm. After the injury his parents noted that he refused to use the arm and complained of pain whenever the arm was touched. Examination revealed extension of the right forearm at the elbow to 175 degrees and flexion to 30 degrees. There was tenderness over the head of the radius. The child held the arm slightly flexed at the elbow with the forearm pronated. X-rays of the extremity were normal. A diagnosis of subluxation of the radial head was made. The dislocation was easily reduced by extension of the forearm at the elbow, followed by supination with pressure over the radial head.

Case 3.—A 4-year-old boy, while playing with his 13-year-old cousin, complained of pain in the left elbow. The parents were unable to give a clear explanation of the mechanism of injury, but the child stated that the cousin twisted his arm. He was seen in the office July 28, 1952, the day after the injury. Examination disclosed tenderness over the head of the radius and pain and limitation of supination of the forearm. Extension and flexion of the elbow were normal. An x-ray of the elbow and forearm was normal. A diagnosis of subluxation of the head of the left radius was made. Reduction was carried out by extension of the elbow, followed by supination of the forearm with pressure over the radial head.

Case 4.—A 2-year-old girl was seen May 27, 1953, because of pain in the left arm and elbow. The mother stated that one week previously, while she was walking downstairs holding the child by the left arm, the child fell, sustaining a pulling injury to the arm. Since the accident the child failed to use the arm normally and complained of soreness about the elbow. Examination revealed supination of the left forearm to be limited, with pain on forcing. Flexion and extension of the elbow were normal. An x-ray of the left upper extremity was made and was normal. A diagnosis of subluxation of the left radial head was made. The forearm was forcibly supinated with the elbow extended, with relief of pain. A posterior plaster splint was applied holding the elbow at 90 degrees flexion and was worn for one week. At the time the splint was removed full supination was present and the child had no pain in the extremity.

Case 5.—A 2-year-old boy was lifted by his left arm on June 5, 1954. The child immediately began to cry and refused to use the extremity. Examination revealed the child to hold the left forearm in pronation. Attempts to move the wrist or elbow were resisted. X-rays were made of both upper extremities and were normal. Forced supination of the forearm resulted in an audible click, and pain was immediately relieved. A plaster splint was applied to the extremity, holding the elbow at 90 degrees. A week later the cast was removed and the child moved the extremity normally and without pain.

Case 6.—A 3-year-old girl was seen in the office July 26, 1958. The day previous, while playing with a water hose in the yard, she had fallen and injured the left arm. After the injury she complained of pain about the elbow and refused to use the arm. Examination revealed that the child held the left forearm pronated with the elbow slightly flexed. There was tenderness over the head of the radius, and supination of the forearm was limited, with pain on forcing. The child was sent to the x-ray department for an x-ray of the elbow, and as the forearm was extended during exposure of the films a slight snap occurred in the region of the head of the radius and pain disappeared. The x-rays of the elbow were normal. A diagnosis of reduced subluxation of the left radial head was made.

Case 7.—A 3-year-old girl was seen Aug. 5, 1958. The mother stated that while playing the child fell, injuring the left arm at the elbow. Examination revealed the left elbow to be held slightly flexed and the forearm pronated. There was no definite tenderness about the elbow, forearm, or wrist. An x-ray was made of the left upper extremity and revealed slight widening of the joint space between the head of the radius and the capitellum of the humerus. A diagnosis of subluxation of the radial head was made. The forearm was extended at the elbow and forcibly supinated, producing a click at the radial head with relief of pain.

Summary

Subluxation of the head of the radius is a traumatic injury occurring in children usually between the ages of 2 and 4 years. The injury is produced by traction on the pronated and extended forearm and causes symptoms of pain in the region of the elbow and limitation of supination of the forearm. X-ray examination may show negative results, but occasionally slight widening of the space between the head of the radius and the capitellum of the humerus is present. Reduction is accomplished by supination of the forearm with the elbow extended, accompanied by slight pressure over the head of the radius and compression of the shaft of the radius against the capitellum of the humerus. A slight click may be palpated as reduction occurs. After reduction the arm should be supported by a sling for several days and traction on the forearm should be avoided for several weeks.

20 Fourth Ave. S. W.

References

1. Griffin, M. E.: Subluxation of Head of Radius in Young Children, Pediatrics **15**:103-106 (Jan.) 1955.

2. Fournier, D.: L'Oeconomie chirurgicale, Paris, F. Clouzier & Cie. 1671, p. 250.

3. Van Arsdale, W. W.: On Subluxation of Head of Radius in Children: With Résumé of One Hundred Consecutive Cases, Ann. Surg. **9**:401-423 (June) 1889.

4. Malgaigne, J.-F.: Traité des fractures et des luxations, Paris, J.-B. Baillière, 1847.

5. Streubel: Ueber die falsche Beurteilung gewisser geringfügiger Verletzungen am Vorderarm kleiner Kinder, Vrtljschr. f.d. prakt. Heilk. **70**:1, 1861.

6. Stone, C. A.: Subluxation of Head of Radius: Report of Case and Anatomic Experiments, J. A. M. A. **67**:28-29 (July 1) 1916.

SPONTANEOUS DISAPPEARANCE OF BILATERAL PULMONARY METASTASES

REPORT OF A CASE OF ADENOCARCINOMA OF KIDNEY AFTER NEPHRECTOMY

Leizor Kessel, M.D., Rocky Hill, Conn.

A 65-year-old man, hospitalized because of general weakness and striking weight-loss, was found by roentgenography to have pulmonary lesions suggesting metastases of a tumor. Intravenous pyelography gave evidence of a malignant tumor of the left kidney. A nephrectomy was performed, and the lesion proved to be a clear-cell serous papillary cystic adenocarcinoma. The condition of the patient remained poor for about three months, and the pulmonary lesions increased in size and number. The patient then improved, and at the time of discharge from the hospital the pulmonary lesions were no longer visible. Similar observations have been made in the past. They suggest the hypothesis that these tumors have distinctive properties as to origin and biological activity.

There are only a few cases reported in the literature of spontaneous disappearance of pulmonary metastases of an adenocarcinoma of the kidney. Mann [1] described three cases in which the metastases were present before nephrectomy and disappeared after the primary tumor was removed. One similar case was reported recently by Arcomano and co-workers [2] in which the metastases present before nephrectomy disappeared eight months after operation. There are two more cases, one reported by Bumpus,[3] the other by Beer,[4] in which the metastases appeared after nephrectomy and disappeared spontaneously about five months later.

The number of these cases is rather low if we take into consideration the facts that kidney tumors constitute about 2% of all malignant tumors in adults and that about 80% of all malignant renal tumors are adenocarcinomas.[5] The reason for this may be the prevailing opinion that nephrectomy in the presence of metastases is a questionable procedure [6] and should be done only if the metastatic lesion is isolated and can be removed at the same time as the kidney. Campbell [7] expressed a similar opinion that nephrectomy is the preferred treatment for renal adenocarcinoma (hypernephroma) in the absence of metastases. Referring to the cases of Mann,[1] Bumpus,[3] and Beer [4] he also recommends nephrectomy when only a single metastasis is present, but without removal of the metastasis.

Report of a Case

A 65-year-old man was admitted with the chief complaints of general weakness and loss of 20 lb. (9.1 kg.) of weight in the four weeks before admission. He had been treated in this hospital in 1952 for a left-sided hemiparesis due to cerebral thrombosis, with complete recovery after six months of treatment. He had had no other diseases until the present admission.

Physical findings on admission were essentially unremarkable. The chest x-ray showed several bilateral nodular densities considered to be metastatic lesions. A series of x-ray studies of bone showed no further metastases. Laboratory findings were essentially within normal limits, except for a leukocyte count of 19,920 per cubic millimeter with a normal differential count, and 12 erythrocytes per high-power field in the urine sediment.

In search for a primary tumor intravenous pyelography was performed and the findings showed evidence of a malignant tumor of the left kidney. A nephrectomy was performed and a clear-cell serous papillary cystic tumor (papillary adenocarcinoma) was found. The patient's general condition remained poor for three months postoperatively. A roentgenogram of the chest made two months after surgery showed the metastatic nodules increased in size and number (fig. 1). During the next several weeks the patient started to improve slowly and a chest x-ray made three months after operation showed striking regression of the multiple nodular lesions. The patient continued to improve and gained 20 lb. in weight. A chest x-ray made four months after operation showed complete clearing of both lung fields. The patient was discharged and was followed up on an outpatient basis. The last roentgenogram of the chest, made seven months after operation, showed both lung fields to remain clear (fig. 2).

From the State Veterans Hospital.

Comment

Adenocarcinomas of the kidney are classified into three groups [6]: (1) serous papillary cystic tumor (papillary adenocarcinoma) with clear cells or with granular cells, (2) malignant cystadenoma, and (3) alveolar carcinoma. These tumors differ to some extent as to the degree of malignancy. The papillary adenocarcinoma with clear cells, previously called hypernephroma,[7] constitutes the most frequent type of renal tumor.[6] It is interesting that, in all reported cases in which the pulmonary metastasis disappeared after nephrectomy, the kidney tumor was a clear-cell adenocarcinoma. This could lead to the assumption that these tumors may be different in origin and biological activity from other adenocarcinomas of the kidney, as they are less malignant, grow slowly, and often become very large before causing any symptoms.

It is known that metastasis of choriocarcinoma (chorioepithelioma) to the lung may also disappear after removal of the primary tumor.[8] Peterson [8a] first suggested that this may be due to specific antibodies (syncytiolysins), which are produced when chorionic cells reach the maternal blood

stream during pregnancy or labor. Bumpus,[3] referring to Peterson's theory of lysins, suggested that the same theory could also be applied to the cases of hypernephromas in which the pulmonary metastases disappeared spontaneously.

It can be assumed that during operation some microscopic parts of the tumor reach the blood stream and cause the production of antibodies (lysins). Some of the particles may develop into metastases before the titer of the antibodies has reached a level sufficient to dissolve them; they are, however, dissolved later, when the titer has increased to a high enough level. This would explain the cases reported by Bumpus [3] and Beer [4] in which the metastases appeared after nephrectomy and disappeared about five months later.

Sometimes the metastases do not appear at all after operation in spite of extension of tumor tissue into the renal veins (eight cases mentioned by Bumpus [3]). In these cases the titer of the antibodies probably increased so fast that the small particles which reached the blood stream during surgery were dissolved before they could grow. It is even more probable that small amounts of antibodies were present in blood before operation, as small tumor particles may break into the blood stream under normal conditions. The titer of these antibodies would be low before nephrectomy because of reaction to the primary tumor; but after nephrectomy, the titer would be high enough to dissolve the particles reaching the blood stream during operation and thus prevent metastases.

It was also observed that the general condition of almost all patients in the described cases was poor for several months after nephrectomy. This

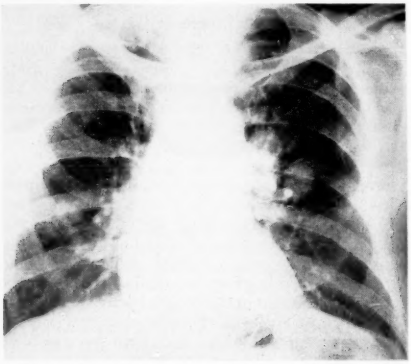


Fig. 1.—Roentgenogram of the chest made two months postoperatively, showing enlarged metastatic nodules.

could be due to increased amounts of toxic products from the destroyed tumor cells. The morbidity of the patients before nephrectomy could also be due to these toxic products rather than to toxins produced by the tumor cells as is generally supposed.

The case presented by Arcomano and co-workers [2] is interesting because the patient developed a metastasis to the brain one year after the disappearance of the pulmonary metastases. This single metastasis was removed and the patient

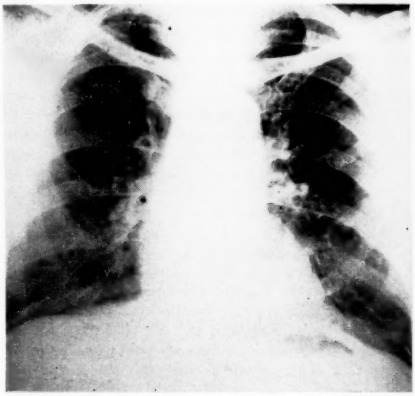


Fig. 2.—Roentgenogram of the chest made seven months postoperatively, showing clear lung fields.

remained asymptomatic for 17 months after surgery. If we accept the hypothesis that antibodies are responsible for the disappearance of the pulmonary metastases, then the development of a metastasis to the brain would suggest that the antibodies either cannot pass the blood–brain barrier or are present there in much smaller concentrations than in the blood and, therefore, cannot prevent the growth of the metastatic cells.

The antibody theory of Peterson [5,6] and Bumpus [3] could also explain why in some cases the metastases appear only after many years. An antibody titer which is not high enough to dissolve metastatic cells would still prevent their growth for many years rather than destroy them completely. If for some reason the antibodies disappear from the blood, then these cells are able to develop again and produce metastases.

All these considerations are of hypothetical nature, as in the last 30 years only these few cases have been described in the literature, and further investigations are needed to explain these interesting findings.

State Veterans Hospital, West Street.

Dr. Miriam Liberson, Chief of the Radiology Department, interpreted the roentgenograms.

Dr. Charles E. Jacobson Jr. performed the nephrectomy.

References

1. Mann, L. T.: Spontaneous Disappearance of Pulmonary Metastases After Nephrectomy for Hypernephroma: Four Year Follow-up, J. Urol. **59**:564-566 (April) 1948.

2. Arcomano, J. P.; Barnett, J. C.; and Bottone, J. J.: Spontaneous Disappearance of Pulmonary Metastases Following Nephrectomy for Hypernephroma, Am. J. Surg. **96**:703-704 (Nov.) 1958.

3. Bumpus, H. C., Jr.: Apparent Disappearance of Pulmonary Metastasis in Case of Hypernephroma Following Nephrectomy, J. Urol. **20**:185-191 (Aug.) 1928.

4. Beer, E.: Some Aspects of Malignant Tumors of Kidney (B. A. Thomas Oration), Surg., Gynec. & Obst. **65**:433-446 (Oct.) 1937.

5. Ackerman, L. V., and Del Regato, J. A.: Cancer: Diagnosis, Treatment, and Prognosis, ed. 2, St. Louis, C. V. Mosby Company, 1954, pp. 725-746.

6. Dodson, A. I.: Urological Surgery, ed. 3, St. Louis, C. V. Mosby Company, 1956, pp. 297-324.

7. Urology, edited by M. Campbell, Philadelphia, W. B. Saunders Company, 1954, vol. 2, pp. 972-991.

8. (*a*) Practice of Obstetrics, edited by R. Peterson, Philadelphia, Lea Bros. & Co., 1907, pp. 472-473. (*b*) Johnson, W. R.: Spontaneous and Complete Regression of Extensive Pulmonary Metastases in Case of Chorionepithelioma, Am. J. Obst. & Gynec. **61**:701-704 (March) 1951.

DOUBLE-BLIND EVALUATION OF METHYLPHENIDATE (RITALIN) HYDROCHLORIDE

ITS USE IN THE MANAGEMENT OF INSTITUTIONALIZED GERIATRIC PATIENTS

Fred T. Darvill Jr., M.D., Sedro Woolley, Wash.

The effects of methylphenidate were compared with those of a placebo in 70 senile patients committed to a state institution because of mental disturbances. Neither the patients nor those who rated their behavior (orientation, appetite, continence, cooperativeness, activity, rationality, personal care, and irritability) knew whether a given patient was receiving the drug or the placebo. Among those who received the drug, two dosage schedules were used, the doses being increased weekly until some patients were receiving 60 mg. daily during the sixth week of the study. No significant differences were found between the test and contratest groups as regarded weight, pulse rate, or behavior ratings. A statistically significant lowering of the blood pressure was found among the subjects who received a maximum daily dose of 30 mg. of methylphenidate but was not found among those who received the maximum daily dose of 60 mg. No undesired side-effects were observed in this study, but the drug in the dosages used did not have any convincing effect on the physical or mental status of the patients.

Methylphenidate (Ritalin) hydrochloride, a psychotropic amine, has been evaluated as to its effect in a variety of psychiatric conditions, including depressions of the aged,[1] severe regression,[2] and schizophrenia.[3] Control groups were used in these studies. Benefit was reported in the first two of the above groups as a result of administration of this drug.

Dube and co-workers [4] evaluated 20 senile patients utilizing a double-blind technique and reported that methylphenidate in a dosage of 10 mg. given four times a day definitely improved behavior when compared to reserpine (1 mg. daily) or to placebos. Patients so studied served as their own controls. However, the number of patients studied is too few to permit drawing other than tentative conclusions.

Ferguson and Funderburk [5] have reported methylphenidate to be of value in the management of primarily retarded committed geriatric patients. Davidoff and associates [6] gave the drug to 10 geriatric patients and reported good results in 6. Side-effects (tension and insomnia) were seen in six patients and were especially evident in those who did not show improvement while receiving the drug.

The latter two studies did not use control groups. The rating of subjective phenomena depending primarily on the judgment of the investigators is known to be unreliable and the results subject to question unless the study is carried out with the double-blind technique.[7] This is particularly true in investigating senile behavior, where any degree of attention or interest will frequently result in an improvement in the parameters being evaluated.[8] To date, no serious effect in any organ or system or in blood pressure or pulse rate has been noted with the use of this drug.[9]

From the Northern State Hospital, Sedro Woolley, Wash., and the Department of Medicine, University of Washington School of Medicine, Seattle.

After reviewing the above papers it was felt worthwhile to evaluate the effect of this drug on senile behavior in a controlled fashion, with use of a sufficient number of patients to allow accurate statistical evaluation. Accordingly, a double-blind evaluation of methylphenidate in the management of institutionalized geriatric patients was undertaken.

Method of Study

All patients studied in this series were committed to Northern State Hospital, Sedro Woolley, Wash., by the superior courts of the state of Washington. Sixty of the subjects who completed the course of study were selected from newly admitted patients, 60 years of age and older, sent directly to the medical geriatric admission ward.[10] All newly admitted patients had a complete history and physical examination and a mental status examination; laboratory studies included a white blood cell count, hematocrit value determination, urinalysis, blood urea nitrogen level determination, serologic tests for syphilis, chest x-ray, and electrocardiogram. After the above evaluation was completed, all patients who were diagnosed as having chronic brain syndrome due to cerebral arteriosclerosis or to senility were considered for the study. A study of higher priority was being conducted simultaneously which required the rejection of patients found to have the following physical conditions: angina, past or present; previous myocardial infarction; congestive heart failure, past or present; diabetes mellitus requiring insulin or tolbutamide therapy; chronic renal disease manifested by a blood urea nitrogen level of over 40 mg. %; diastolic hypertension manifested by a sustained diastolic pressure of over 110 mm. Hg; adrenal cortical hypofunction (Addison's disease); and peripheral vascular insufficiency of severe nature. The 60 newly admitted patients finally selected for this study all had one or more of the above physical disabilities; it can be seen, then, that these patients included in this study had poorer physical health than the average geriatric patient admitted to this hospital. Further indication of this selection was the fact that the average age of the patients in this group was 78 years, whereas the over-all average age of the geriatric patients was 74 years on admission.

Ten of the patients who completed the course of study were long-term occupants of geriatric wards. These patients were not screened on the basis of physical disease or laboratory findings and therefore represented the average geriatric patient as far as physical health and metabolic status was concerned. Five additional patients were started on this study but did not complete the eight-week course for reasons to be detailed later.

After a minimum of 10 days of hospitalization, the weight, pulse rate, and blood pressure were determined and the following eight parameters evaluated: orientation, appetite, continence, cooperativeness, activity, rationality, personal care, and irritability. A word description of the baseline state was then entered on the patient's rating sheet. These ratings were made in conference with the ward nurse, the ward physician, the attending staff, and the investigating physician. With the case number used as the sole criterion, these patients were then assigned alternately to either drug A or drug B, one of which was of methylphenidate, 10 mg., and one of which was a physically indistinguishable placebo. No one in the institution was aware of which drug was the active one and which was the placebo. No effort was made to assign patients to the study because of the degree of mental defect present, the degree of activity or retardation, or the findings in any of the evaluated parameters.

In 30 patients (group 1), 24 men and 6 women aged 65 to 91 years, the dosage was as follows: first week, one tablet daily; second week, one tablet twice a day; third to sixth weeks, one tablet three times a day; and, seventh to eighth weeks, no medication. For those patients who received the active drug, the dosage was 10 mg. daily the first week; 20 mg. daily the second week; and 30 mg. daily for the third to sixth weeks.

In 40 patients (group 2), 22 men and 18 women aged 65 to 98 years, the dosage was as follows: first week, one tablet daily; second week, one tablet twice a day; third week, one tablet three times a day; fourth week, one tablet four times a day; fifth week, one tablet five times a day; sixth week, two tablets three times a day; and, seventh to eighth weeks, no medicaments. For those who received the active drug, the dosage was 10 mg. daily the first week and weekly increments of 10 mg. daily were given for the next five weeks, so that the dose on the sixth week of the study was 60 mg. daily.

Toward the end of each of the eight weeks the blood pressure, pulse rate, and weight were again determined and the eight behavior parameters were reevaluated by the same rating team and compared to the base line on the following scale: much improved, some improved, no change, worse, and much worse. At the conclusion of the eight-week period an over-all evaluation of the response to therapy was made, both in words and with the rating scale. Any medical diseases or additional behavioral manifestations occurring during the study were noted.

Results

Of the 75 patients at the start of this study, 70 completed the eight-week course of medication and observation. Two patients, one receiving methylphenidate and one receiving the placebo, died suddenly during the study. Clinically, these

deaths were presumed to be due to coronary artery disease. One patient receiving methylphenidate had a cerebral vascular accident which necessitated cessation of oral drug therapy. One patient receiving the placebo became so agitated that emergency electroshock therapy was imperative. One patient was dropped from the study for treatment of hypothyroidism bordering on myxedema which was suspected clinically but not confirmed before the study was instituted.

In the 30 patients completing the study in group 1, there were no significant medical illnesses occurring in those patients who received methylphenidate. Among those given the placebo, a carbuncle, one case of pneumonia, and one case of paroxysmal supraventricular tachycardia appeared. Of the 40 patients in group 2, one case of bronchitis, one case of lethargy, and one grand mal epileptic seizure were noted in the patients treated with methylphenidate. Two cases of pneumonia and one case of congestive heart failure were noted in the placebo group.

Over-all Response to Methylphenidate and Placebo Therapy in Geriatric Patients

	Much Improved, No.	Some Improved, No.	No Change, No.	Some Worse, No.	Much Worse, No.
Group 1					
Placebo	2	5	7	1	0
Methylphenidate	2	3	8	2	0
Group 2					
Placebo	1	6	10	3	0
Methylphenidate	2	4	12	1	1

No significant changes occurred in weight or pulse rate in either the experimental or control group. In group 1 (but not group 2) a significant ($p=0.01$) reduction in blood pressure occurred in the group treated with methylphenidate, as compared to the group treated with the placebo.

No statistically significant differences in any of the evaluated parameters could be demonstrated between the experimental and control groups in either dosage range. No statistically significant difference could be detected in the over-all response between the experimental and control groups in either dosage range. The table details the over-all response in both groups.

Comment

It is apparent that, in this group of elderly, senile, institutionalized patients, methylphenidate in adequate doses was of no value in improving the senile state. The improvement noted on previous studies and in this study was most likely due to the increased attention and interest which the patients received when selected for study. The need to carefully control studies in evaluating drugs of all kinds, and particularly drugs which may improve or influence the senile state, is again demonstrated.

The blood pressure change noted in group 1 is interesting, and it is suggestive that this drug may conceivably act as an antihypertensive agent. However, no blood pressure change of significance was noted in group 2. Although the blood pressure changes noted were statistically significant, it seems probable that these changes were coincidental. Further study is needed in this regard.

Summary

Seventy senile, institutionalized patients were studied with use of the double-blind technique during treatment with methylphenidate (Ritalin) hydrochloride and an identical placebo. No significant toxicity was noted in two groups receiving different dosages. No statistically significant improvement in the senile state could be demonstrated as a result of such treatment with methylphenidate.

809 S. 15th St., Mount Vernon, Wash.

This study was supported by a grant from Ciba Pharmaceutical Products, Inc.

The statistical evaluations were performed by Dr. B. M. Bennett, Department of Public Health and Preventive Medicine, University of Washington School of Medicine.

References

1. Jacobsen, A.: Use of Ritalin in Treating Depressions of Aged, abstracted, J. Gerontol. **11:**443 (Oct.) 1956.

2. Sommerness, M. D., and Lucero, R. J.: Pilot Study of Effects of Stimulant Drugs on Regressed Patients, Minnesota Med. **40:**831-833; 839 (Dec.) 1957.

3. McPheeters, H., and Fox, W. W.: Evaluation of Reserpine and Methyl Phenidylacetate Used Separately and in Combination in Chronic Psychotic Patients, J. Kentucky M. A. **54:**785-791 (Sept.) 1956. Madi, M. L., and Kovitz, B.: Experiences with Methyl-phenidylacetate Hydrochloride (Ritalin) in Psychotic Patients, Antibiotic Med. **3:**309-311 (Oct.) 1956.

4. Dube, A. H.; Osgood, C. K.; and Notkin, H.: Effects of Analeptic (Ritalin) and Ataraxic (Reserpine), and Placebo in Senile States, J. Chron. Dis. **5:**220-234 (Feb.) 1957.

5. Ferguson, J. T., and Funderburk, W. H.: Improving Senile Behavior with Reserpine and Ritalin: New Approach with Use of Methyl Phenylpiperidylacetate, J. A. M. A. **160:**259-263 (Jan. 28) 1956.

6. Davidoff, E.; Best, J. L.; and McPheeters, H. L.: Effect of Ritalin (Methyl-phenidylacetate-Hydrochloride) on Mildly Depressed Ambulatory Patients, New York J. Med. **57:** 1753-1757 (May 15) 1957.

7. Koteen, H.: Use of "Double-Blind" Study Investigating Clinical Merits of New Tranquilizing Agent, Ann. Int. Med. **47:**978-989 (Nov.) 1957.

8. Clark, L. D.: Evaluation of Therapeutic Effects of Drugs on Psychiatric Patients, Dis. Nerv. System **17:**282-286 (Sept.) 1956.

9. Ferguson, J. T.: Further Evaluation of New Drug, Methyl-phenidylacetate, in Treating Mentally Ill, abstracted, J. Pharmacol. & Exper. Therap. **116:**20 (Jan.) 1956.

10. Darvill, F. T., Jr., and Jones, C. H.: Evaluation of Medical Admission Ward for Old Patients in Psychiatric Hospital, Geriatrics **13:**587-593 (Sept.) 1958.

MEPHENTERMINE SULFATE FOR TREATMENT OF ARTERIAL HYPOTENSION

Travis Winsor, M.D., Los Angeles

The possibility of using mephentermine sulfate to treat various types of hypotension was studied in three groups of patients. Group 1 consisted of 10 patients who had hypotensive episodes during a rigorous course of treatment for essential hypertension or hypertensive renal disease. Group 2 consisted of 10 patients who had hypotensive episodes related either to diabetes or to cerebral arteriosclerosis. Group 3 consisted of 10 patients with a variety of nonspecific hypotensive syndromes. Measurements of blood pressure, of maximum ventricular excursion by roentgenkymography, of the I-J wave in ballistocardiograms, of blood flow in the finger, and of peripheral vascular resistance showed that mephentermine in the dosages used corrected the hypotension by both central and peripheral action. It was active when given orally, intramuscularly, or intravenously. For the type of hypotension seen in group 2, a daily oral dose of 12.5 mg. after the morning or noonday meal usually sufficed.

Hypotension may be caused by or associated with diabetes, cerebrovascular insufficiency, and a miscellaneous group of other diseases commonly characterized by a tendency to lethargy, fatigability, daytime drowsiness, and postural dizziness. The same symptoms also are produced in a certain percentage of patients by the ganglion-blocking agents, although considerable research has been directed toward reducing the severity of this complication to antihypertensive treatment. Trimethidinium methosulfate, for example, one of the newer asymmetric bisquaternary compounds (fig. 1), which exerts a potent ganglioplegic activity, induces postural hypotensive symptoms in about the same incidence as do other ganglion blockers. Its formula is d-[N-methyl-N-(γ-trimethylammoniumpropyl)] 1-methyl-8,8-dimethyl-3-azobicyclo [3.2.1] octane dimethosulfate. Parenteral or oral dosage, in the usually recommended range, exerts ganglioplegic activity for approximately 12 hours.

Mephentermine sulfate (N,α,α-trimethylphenethylamine sulfate) is a sympathomimetic pressor amine. This compound produces an antiarrhythmic [1] and positive inotropic action and also vasoconstriction.[2] In dogs, coronary flow has been increased under constant coronary perfusion pressures.[3] Mephentermine may be administered orally or parenterally and has been used clinically for prevention or treatment of hypotension associated with spinal anesthesia [4] and for correction of depressed blood pressure associated with shock in myocardial infarction [5] and obstetric delivery.[6]

The present study was designed to determine the effectiveness of mephentermine in controlling an excessive hypotensive response to the ganglionic blocking agent, trimethidinium methosulfate, and management of hypotension in a variety of other conditions.

Methods and Materials

The series consisted of 45 outpatients 23 to 72 years old, with an average of 49 years. Eighty per cent were men.

Group 1 (table 1) comprised 10 patients (7 men and 3 women), with an average age of 48 years, who had essential hypertension or whose elevated blood pressure was caused by polycystic kidney disease, glomerulonephritis, or obstruction of the renal artery (Goldblatt's hypertension). Retinopathy of grade 2 or 3 severity, according to the Keith-Wagener criteria, was present in every case. All had been maintained on a low-sodium diet and had been receiving diuretics and Rauwolfia serpentina. Trimethidinium methosulfate also had been administered orally, on a fasting stomach, at intervals of 12 hours, for one to five months. Total daily dosages ranged from 40 to 120 mg., with an average of 60 mg. Under this regimen most of the patients obtained reduction in blood pressure but occasionally experienced postural hypotension three to four hours after the morning medication. When hypotensive symptoms occurred during the course of trimethidinium therapy, 30 mg. of mephentermine was administered intramuscularly; later a dose of 25 mg. was administered orally for each hypotensive episode. The blood pressure was then read at intervals for two hours.

Group 2 (table 2) consisted of 10 patients, 4 with diabetes and 6 with cerebrovascular insufficiency caused by arteriosclerosis. In these patients orthostatic hypotension was particularly troublesome during hot weather, during convalescence from infection or operation, and in the presence of fatigue. During hypotensive periods 25 mg. mephentermine was administered orally after breakfast each morning.

Of the 10 patients in group 3 who had nonspecific hypotensive syndromes, 4 had neurasthenia, 3 were suffering from malignant processes, 2 had chronic infections, and 1 was convalescing after operation.

From the Department of Medicine, University of Southern California School of Medicine, and the Heart Research Foundation.

Orthostatic hypotension, with postural dizziness, depression, and lethargy, was episodic and aggravated by heat and fatigue. The control blood pressure with the patients standing averaged 92 mm. Hg systolic (range, 88 to 100) and 55 mm. Hg diastolic (range, 42 to 62). Mephentermine was administered orally, in a dose of 25 mg., after breakfast.

Determinations of Blood Pressure, Cardiac Output, and Pulse Volume.—Segmental and digital plethysmograms were taken with equipment previously described.[7] Roentgenkymograms were recorded with the Liebel-Flarsheim kymograph. Ballistocardiograms were taken with the Nickerson low-frequency standardized table. Blood pressure was determined with a mercury manometer or with the Colson automatic blood pressure recorder.

Orthostatic hypotension was arbitrarily defined as blood pressure, with the patient in the standing position, of 100 mm. Hg systolic or less and 60 mm. Hg diastolic or less.

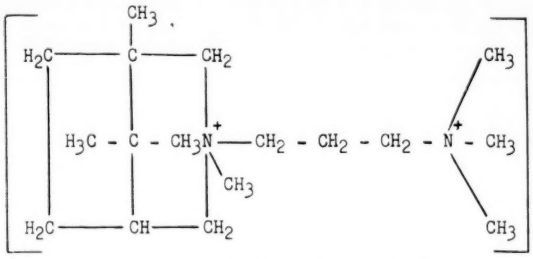


Fig. 1.—Trimethidinium methosulfate.

Results

Group 1 (table 1).—After administration of mephentermine, a rise in blood pressure occurred for all patients in group 1, in both standing and supine positions. The highest pressure with the patient standing is listed for each in table 1. Most patients were symptomatically improved; weakness and dizziness were eliminated or diminished.

The blood pressure response of the patient in case 6 is shown in figure 2. The hypotension was demonstrated by segmental plethysmographic record taken from the arm (fig. 3). With the patient in the supine position, the arm cuff was inflated to 100 mm. Hg (pressure at which the maximum pulsation was obtained). The blood pressure was 160/100 mm. Hg; the amplitude of the pulse curve was 0.6 cc. per pulse. As soon as the patient assumed the standing position, with the same pressure in the cuff, the amplitude was 0.1 cc. per pulse. On prolonged standing the amplitude of pulsation was reduced. One hour after intramuscular administration of 30 mg. of mephentermine the cuff was inflated to 115 mm. Hg (pressure at which the maximum pulsation was obtained). With the patient supine, the blood pressure was 185/115 mm. Hg and the pulse volume 0.93 cc. per pulse. As soon as the patient stood, the pulsation was reduced to 0.5 cc. per pulse and the blood pressure to 120/80 mm. Hg.

Group 2 (table 2).—A definite increase occurred in systolic and diastolic blood pressure with the patients standing as well as in the supine position. Three patients reported that they experienced less dizziness on standing, two were less fatigued during the day, three had less daytime drowsiness, and two reported subsidence of depression. On the 25-mg. dose, two patients reported nervousness and two insomnia and one each experienced quivering, vertigo, and nausea. For these the dose was reduced to 12.5 mg., after which there were no side-effects. Five of the group continued taking mephentermine in daily doses of 12.5 mg. for four months. A satis-

TABLE 1.—*Effect of Mephentermine on Orthostatic Hypotension Produced by Trimethidinium*

Case No.	Age, Yr.	Sex	Diagnosis	Blood Pressure, Mm. Hg: During Trimethidinium Treatment, Supine, Systolic	Supine, Diastolic	Standing, Systolic	Standing, Diastolic	After 1M Dose of Mephentermine, Supine, Systolic	Supine, Diastolic	Standing, Systolic	Standing, Diastolic
1	48	M	Essential hypertension	120	90	90	60	150	95	120	88
2	55	M	Essential hypertension	150	100	98	65	170	108	130	95
3	60	F	Essential hypertension	185	102	100	70	172	104	120	85
4	50	M	Essential hypertension	158	95	102	60	162	100	124	86
5	45	M	Essential hypertension	159	100	98	65	180	110	138	90
6	38	F	Essential hypertension	160	100	90	60	185	115	120	88
7	39	M	Polycystic kidney disease	149	101	90	70	160	102	148	98
8	14	M	Glomerulonephritis	128	98	98	72	148	99	140	90
9	48	F	Glomerulonephritis	128	85	99	62	130	90	120	82
10	50	M	Obstruction of renal artery	138	90	100	70	140	100	128	99
Mean	47.7	M-7; F-3		147.5	96.1	96.5	65.4	159.7	102.3	128.8	90.1
Minimum				120	85	90	60	130	90	120	82
Maximum				185	102	102	72	185	115	148	99

factory antihypotensive action was maintained throughout this period; no tachyphylaxis occurred.

Figure 4 shows the effect of mephentermine on the blood pressure of the patient in case 17 (table 2) after an oral dose of 12.5 mg. taken in the fasting state. The blood pressure rose from 110/68 to 118/73 mm. Hg. Similar results were obtained in five patients (table 1) whose blood pressure was determined with the Colson recorder.

Group 3.—One hour after the oral dose of mephentermine the systolic blood pressure averaged 107 mm. Hg (range, 98 to 118) and the diastolic 64 mm. Hg (range, 52 to 78). For three patients the dose of mephentermine was reduced to 12.5 mg., since the 25-mg. dose seemed excessive and had induced some nausea or nervousness.

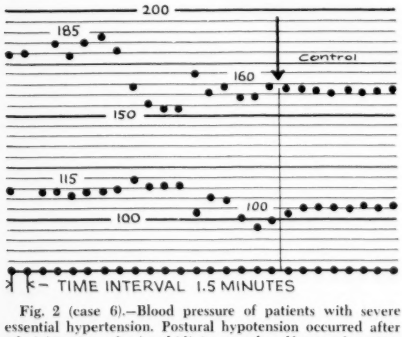


Fig. 2 (case 6).—Blood pressure of patients with severe essential hypertension. Postural hypotension occurred after administration of trimethidinium methosulfate and patient was dizzy on standing; hypotensive symptoms were controlled by intramuscular injection of 30 mg. of mephentermine. Arrow indicates time of injection. Read record from right to left.

Mechanism of Action.—The mechanism of action was studied by observing the effects of mephentermine on the heart, as recorded on the roentgenkymogram and the ballistocardiogram, and on the peripheral circulation by determination of the finger blood flow and local peripheral resistance.

A roentgenkymogram was taken for five patients. The maximum amplitude of pulsation of the left ventricular border was recorded before administration of mephentermine and one hour after intramuscular injection of 25 mg. (table 3). The studies made before antihypotensive medication were done during episodes of orthostatic hypotension. The roentgenograms were taken with the patient in the standing position. A definite increase occurred in the amplitude of pulsation one hour after administration of the dose.

Ballistocardiograms were taken for five patients, three with diabetes and two with cerebrovascular insufficiency (table 4). All had a tendency toward hypotension in the supine position. The height of the I-J wave was measured in millimeters before administration of mephentermine and one hour after intramuscular injection of 25 mg. In all cases the amplitude of the I-J wave increased after the injection.

Finger flow and peripheral resistance were measured in five patients, three of whom had Raynaud's disease, for which sympathectomy affecting the upper extremities had been done. Two had thromboangiitis obliterans. The blood pressure was recorded by the auscultatory method, with use of a mercury manometer at the elbow. Finger flow

TABLE 2.—*Effect of Mephentermine on Orthostatic Hypotension Associated with Diabetes and Cerebrovascular Insufficiency*

Case No.	Age, Yr.	Sex	Diagnosis	Blood Pressure, Mm. Hg: Control, Supine, Systolic	Control, Supine, Diastolic	Control, Standing, Systolic	Control, Standing, Diastolic	After Oral Dose of Mephentermine, 25 Mg., Supine, Systolic	After Oral Dose of Mephentermine, 25 Mg., Supine, Diastolic	After Oral Dose of Mephentermine, 25 Mg., Standing, Systolic	After Oral Dose of Mephentermine, 25 Mg., Standing, Diastolic
11	34	F	Diabetes	110	80	100	70	114	82	110	80
12	29	F	Diabetes	119	82	100	75	122	88	115	80
13	68	M	Diabetes	112	72	98	70	122	80	120	79
14	70	M	Diabetes	119	80	100	71	134	88	120	82
15	62	F	Cerebrovascular insufficiency	100	65	95	58	130	72	112	76
16	60	M	Cerebrovascular insufficiency	98	64	90	55	110	70	108	70
17	58	M	Cerebrovascular insufficiency	110	68	90	59	128	80	120	75
18	47	M	Cerebrovascular insufficiency	108	72	95	60	124	76	118	70
19	50	M	Cerebrovascular insufficiency	100	65	95	60	114	74	110	70
20	42	M	Cerebrovascular insufficiency	102	68	98	68	118	78	110	74
Mean	52.0	M-7; F-3		107.8	71.6	96.7	65.5	120.6	79.7	114.3	76.5
Minimum	29			98	64	90	55	110	74	108	70
Maximum	70			119	82	100	79	134	88	120	82

TABLE 3.—*Mechanism of Action of Mephentermine for Correction of Hypotension: Results of Roentgenkymography of Chest*

Case No.	Diagnosis	Maximum Excursion Left Ventricle (Mm.): Before Mephentermine	After IM Dose of Mephentermine, 25 Mg.
21	Diabetes	3.0	4.0
22	Diabetes	2.5	3.5
23	Diabetes	2.5	3.5
24	Cerebrovascular insufficiency	3.0	4.5
25	Cerebrovascular insufficiency	2.5	3.5
Mean		2.7	3.8
Minimum		2.5	3.5
Maximum		3.0	4.5

was determined with a vein-occluding digital cuff. Peripheral resistance was calculated by taking the sum of the systolic blood pressure and twice the diastolic pressure, dividing by 3 to obtain the mean arterial pressure, and inserting this figure into the formula, as follows: Mean pressure in millimeters of mercury÷blood flow in cubic millimeters per 4 cc. of digit per second=the peripheral resistance units (PRU).

Comment

The positive inotropic action of mephentermine has been demonstrated by Freiheit [8] and others.[9] Oppenheimer [10] has shown that this compound decreases the refractory period and increases the conduction velocity in the cardiac muscle. A peripheral effect of mephentermine is suggested by the beneficial action of the compound when it is used in conjunction with spinal anesthesia.[4]

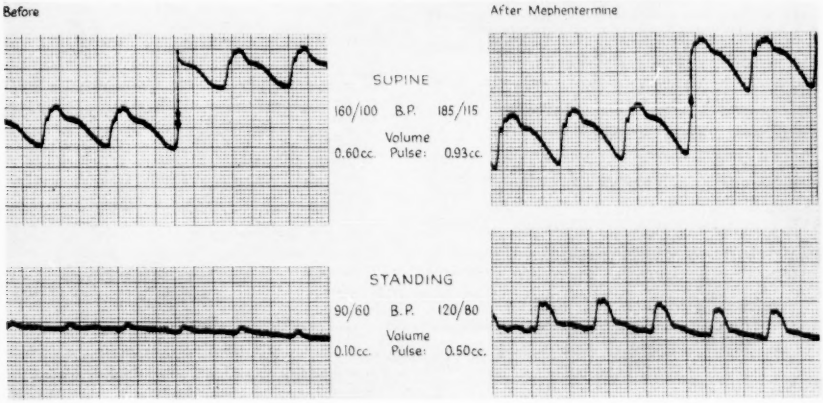


Fig. 3 (case 6).—Pulse volume in arm before and after administration of mephentermine. Standardization represents volume change of 1 cc.

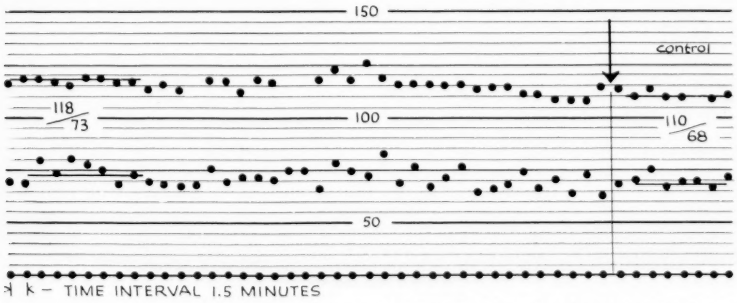


Fig. 4 (case 17, table 2).—Effect on blood pressure of oral dose of 12.5 mg. of mephentermine administered on fasting stomach (read from right to left).

Measurements made before administration of mephentermine and one hour after intramuscular injection of 25 mg. showed decrease in blood flow with increase in peripheral resistance (table 5).

As a result of the antihypotensive medication, there was a definite decrease in the amplitude of pulsation in the digit from an average of 2.0 to 0.5 cu. mm. per pulse. A typical record is that of the patient in case 32 (table 5), which is shown in figure 5.

The findings in this study indicate that mephentermine is useful for correction of hypotension from various causes and that the mechanism of action is both central and peripheral. The excursion of the left ventricular pulse and the force of the cardiac contraction were increased, and there was a mild increase in the local peripheral resistance and decrease in the amplitude of the pulsation at the fingertip. A positive inotropic and a peripheral action were induced by intramuscular injection of

25 mg. of the compound. This dose is small in comparison with that used for reversal of acute shock in myocardial infarction. In such cases an initial intramuscular or intravenous injection of 50 mg. is often required to return the blood pressure to normotensive levels.

The usefulness of mephentermine has been demonstrated for treatment of hypotensive episodes during medication with ganglionic blocking agents.

TABLE 4.—*Data from Ballistocardiogram Taken Before and After Intramuscular Injection of Mephentermine*

Case No.	Diagnosis	Height of I-J Wave (Mm.) Before	After 25 Mg. IM
26	Diabetes	3.0	5.0
27	Diabetes	4.5	7.5
28	Diabetes	5.0	6.5
29	Cerebrovascular insufficiency	4.5	7.0
30	Cerebrovascular insufficiency	6.0	9.0
	Mean	4.6	7.0
	Minimum	3.0	5.0
	Maximum	6.0	9.0

When symptoms of postural hypotension are severe the compound should be administered intramuscularly or intravenously. For mild symptoms the oral form is adequate.

Hypotension associated with diabetes or cerebrovascular insufficiency often can be treated adequately with a daily oral dose of 12.5 mg. of mephentermine, administered after breakfast. This dose is well tolerated, appears not to produce tachyphylaxis, and is usually sufficient to support the blood pressure of patients who exhibit a nonspecific hypotensive syndrome.

Since mephentermine exerts a prolonged activity (e. g., in this series a dose of 12.5 to 25 mg. sufficed for 12 to 24 hours), the compound should not be taken later than 4 p. m. because of the possibility of insomnia. The larger the dose, the longer is the action and the greater the tendency toward sleeplessness. In properly adjusted dosage, mephentermine medication may be continued indefinitely.

The cardiac output, pulse volume, and peripheral resistance were measured by segmental and digital plethysmograms, roentgenkymograms, and ballistocardiograms; the blood pressure was recorded with a mercury manometer or the Colson automatic recorder. Orthostatic hypotension was defined as

TABLE 5.—*Finger Blood Flow and Peripheral Resistance Before and After Intramuscular Injection of Twenty-five Milligrams of Mephentermine*

Case No.	Diagnosis	Brachial Blood Pressure, Mm. Hg Before	After	Finger Flow, Cu. Mm./4 Cc./Second Before	After	PRU* Before	After
31	Raynaud's disease	130/70	150/85	14	2.0	6.4	58.3
32	Raynaud's disease	120/82	148/90	7	1.5	13.5	72.9
33	Raynaud's disease	128/82	158/98	12	1.0	8.1	118.0
34	Thromboangiitis obliterans	110/68	150/92	19	4.0	4.3	27.8
35	Thromboangiitis obliterans	118/78	160/102	24	6.0	3.8	20.3
	Mean	121/76	153/93	15.2	2.9	7.2	58.5
	Minimum	110/70	148/85	7	1.0	3.8	20.3
	Maximum	130/82	160/102	24	6.0	13.5	118.0

* PRU = Peripheral resistance unit.

systolic pressure of 100 mm. Hg or less and diastolic pressure of 60 mm. Hg or less with the patient in the standing position.

Intramuscular injection of 25 to 30 mg. of mephentermine sufficed to counteract the excessive response to a ganglionic blocker. For mild symptoms the orally given form was adequate. For hypotension associated with diabetes, cerebrovascular insufficiency, or other conditions, a daily oral dose of 12.5 mg. after a meal was sufficient; for severe symptoms 25 mg. might be required. In properly adjusted dosage, mephentermine medication may be continued indefinitely.

The mechanism of action of mephentermine is both central and peripheral. Intramuscular injection of the compound produces a positive inotropic action and induces a mild increase in local peripheral resistance with decrease in the amplitude of the pulsation at the finger tip. The pressor activity is prolonged; hence, the dose should not be administered after 4 p. m. because of the possibility of insomnia.

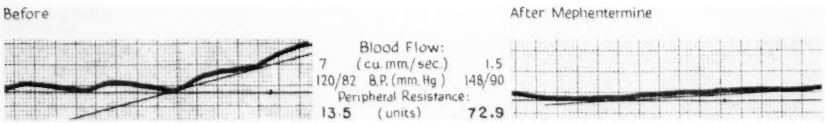


Fig. 5 (case 32, table 5).—Effect of mephentermine on finger blood flow and peripheral resistance.

Summary

Hypotension may be caused by or associated with a variety of diseases in which abnormality of the cardiovascular system is involved and may attend use of the ganglionic blocking agents. Mephentermine sulfate was given intramuscularly to 45 adult patients to correct an excessive response to use of trimethidinium methosulfate and orally, after a meal, to control hypotension associated with diabetes, arteriosclerotic cerebrovascular insufficiency, and a variety of nonspecific hypotensive syndromes.

3875 Wilshire Blvd. (5).

The mephentermine sulfate used in this study was supplied by Wyeth Laboratories, Los Angeles.

This study was supported, in part, by a grant from the Ventura County (Calif.) Heart Association.

Sally Cody supplied technical assistance in this study.

References

1. Bernstein, A.; Cohen, F.; Robins, B.; and Simon, F.: Treatment of Arrhythmias and Shock with Mephentermine Sulfate in Large Doses, J. Newark Beth Israel Hosp. **9:**3-14 (Jan.) 1958. Lynch, P. R.; Webber, D. L.; and Oppenheimer, M. J.: Mephentermine as Antifibrillatory Drug Against Cyclopropane-Epinephrine Ventricular Fibrillation, Anesthesiology **16:**632-642 (July) 1955. Cummings, J. R., and Hays, H. W.: Cardiovascular Studies of Adrenergic and Ganglionic Stimulating Drugs Administered During Cyclopropane, ibid. **17:**314-324 (March) 1956.

2.(*a*) Eckfeld, D. K.; Abell, L. L.; and Seifter, J.: Pharmacological Properties of Mephentermine, Sympathomimetic Amine, J. Am. Pharm. A. (Scient. Ed.) **43:**705-708 (Dec.) 1954. (*b*) Brofman, B. L.; Hellerstein, H. K.; and Caskey, W. H.: Mephentermine—Effective Pressor Amine: Clinical and Laboratory Observations, Am. Heart J. **44:**396-406 (Sept.) 1952. (*c*) Walkenstein, S. S.; Chumakow, N.; and Seifter, J.: Detoxication and Excretion of Mephentermine, J. Pharmacol. & Exper. Therap. **115:**16-20 (Sept.) 1955.

3. Welch, G. H., Jr.; Braunwald, E.; Case, R. B.; and Sarnoff, S. J.: Effect of Mephentermine Sulfate on Myocardial Oxygen Consumption, Myocardial Efficiency and Peripheral Vascular Resistance, Am. J. Med. **24:**871-881 (June) 1958. Reference 2*b*.

4. Anderson, B. M., and Matzinger, P.: Effect of Mephentermine Sulfate as Prophylactic Vasoconstrictor for Spinal Anesthesia, Anesth. & Analg. **35:**234-241 (May-June) 1956. Smessaert, A., and Collins, V. J.: Use of Mephentermine as Pressor Agent During Spinal Anesthesia, Anesthesiology **16:**795-800 (Sept.) 1955. Blundell, A. E.; Pillion, J. W.; and Ansbro, F. P.: Mephentermine—Clinically Useful and Effective Pressor Amine, Anesth. & Analg. **35:**483-488 (Sept.-Oct.) 1956.

5. Hellerstein, H. K.; Brofman, B. L.; and Caskey, W. H.: Shock Accompanying Myocardial Infarction: Treatment with Pressor Amines, Am. Heart J. **44:**407-427 (Sept.) 1952.

6. Hingson, R. A.; Davis, H. S.; Inman, C. E.; and Le Lievre, R. E.: Clinical Evaluation of Mephentermine as Vasopressor in Surgery and Obstetrics, Am. Pract. & Digest Treat. **6:**1004-1014 (July) 1955.

7. Winsor, T.: Segmental Plethysmograph, Angiology **8:**87-101 (Feb.) 1957; Clinical Plethysmography: Improved Direct Writing Plethysmograph, ibid. **4:**134-148 (April) 1953.

8. Freiheit, H. J.: Preliminary Observations on Positive Inotropic Effects of Mephentermine, Internat. Rec. Med. **170:**510-514 (Sept.) 1957.

9. Glassman, J. M., and Seifter, J.: Effect of Mephentermine on Hypodynamic and Arrhythmic Isolated Frog Hearts, J. Pharmacol. & Exper. Therap. **112:**364-373 (Nov.) 1954.

10. Oppenheimer, M. J.; Lynch, P. R.; and Ascanio, G.: Action of Mephentermine on Arrhythmias Due to Pulsus Alternans, Rapidly Discharging Single Atrial Foci and Prolonged P-R Intervals, Am. J. Physiol. **191:**481-486 (Dec.) 1957.

CLINICAL NOTES

SWEAT BAND DERMATITIS—REPORT OF THREE CASES

George E. Morris, M.D., Boston

Sweat band dermatitis has not recently been described in the medical literature of the United States, and one of the underlying reasons for its low incidence is the fact that chrome-tanning compounds are not used in the preparation of sweat bands. Therefore, the leather of sweat bands contains, if any, only a limited amount of chromium. The vegetable tannins which are used are not potent sensitizers.

The use of chrome-tanned leather in sweat bands obtained under its procurement program has been specifically prohibited by the United States government in the two pertinent specifications which are now in force. "Military Specification MIL-B-3577A (S&A), Jan. 19, 1954, Band, Sweat, Cap (Leather)," which covers the requirements for sweat bands used in caps worn by military personnel, states that "chrome-tanned leather will not be permitted." "Interim Federal Specification GG-H-00166a (GSA-FSS), April 18, 1956, Headbands, Mirror," which covers mirror headbands for use by practitioners and specialists, states that "the leather shall be well tanned with vegetable tanning materials."

Member, Committee on Occupational Dermatoses, Council on Industrial Health, the American Medical Association.

These governmental restrictions, as well as the self-imposed restrictions of the larger manufacturers of sweat bands in the United States, against the use of chrome-tanned leather now appear to have been in the best interests of the public. For it has now been established [1] that the lactic acid and lactate portions of human perspiration can leach chrome salts from chrome-tanned leather and deposit them onto the skin and that sensitization dermatitis can result from the basic chromic sulfate—$[Cr(H_2O)_5OH]\ SO_4$—thus deposited on the skin. Considering the uniquely close contact of the sweat band with the forehead, it would have been inevitable, had these restrictions not been in effect, that some persons would have developed dermatoses from this trivalent chromium sensitizer. This basic chromic sulfate is not related to either chromates or dichromates, as is evident from figure 1. The soluble chromates and dichromates form yellow and orange solutions for the most part, whereas the basic chromic sulfate salt found in chrome-tanned leather forms a green solution.

This basic chromic sulfate compound is now available for patch-testing purposes and has caused positive patch-test reactions in a 0.2% solution.[1] It is the chemical that should be used if one suspects

that the chromium of the leather is the cause of a person's dermatitis. There is neither chromate nor dichromate in shoe leather. The leaching of basic chromic sulfate by the lactic acid and lactate portions of the perspiration has caused dermatoses of the hands and feet from the wearing of chrome-tanned leather gloves and shoes in sensitized persons.[2]

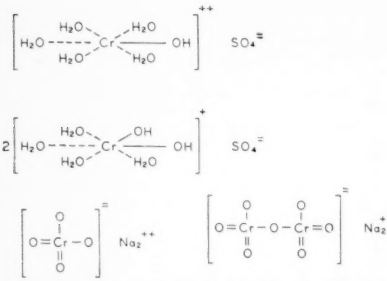


Fig. 1.—Formulas of complex coordination compounds found in a chrome-tanned leather: (*top*) one-third basic; (*center*) two-thirds basic; (*bottom left*) chromate ion; and (*bottom right*) dichromate ion.

Chemical analysis of a nurse's stockings (whose white shoes had shown green chrome-discoloration) has shown that they contained a considerable quantity of trivalent chromium salts. This is the first report of the finding of trivalent chromium salts in stockings. The sample was extracted in a Soxhlet extractor with water and the extract concentrated. A qualitative test for hexavalent chrome was run with use of diphenylcarbazide as a reagent. This test gave negative results. A portion of the extract was then dried down and oxidized to the hexavalent form and the diphenylcarbazide test repeated. In this case there was a very strong positive reaction for hexavalent chrome. This means that in the stocking there was practically a complete absence of hexavalent chrome but a considerable quantity of trivalent chrome.

Chromium salts, however, are rarely used in the tanning of sweat bands in the United States, and the only recent cases of sweat band dermatitis that have been reported (both were in the foreign literature) have been described as being due to Thioprene latex used as a sizing agent in paper or cloth sweat bands [3] or as being due to a laurel oil with which some hats are treated.[4]

This report deals with three cases of typical sweat band dermatitis seen in my practice, one from paper and the other two from rubbing substances onto the sweat band by the hands.

Report of Cases

Case 1.—A worker in a cordage plant developed a generalized dermatitis (extending from his neck to his feet) from the oiled fibers of the rope. He was kept out of work, given treatment, and completely cleared of his eruption. He was told to destroy all his old clothing, and new protective clothing was supplied. He returned to work and was seen one week later with a dermatitis of the sweat band area. The only article of clothing he had not discarded was an old hat that he was accustomed to wear at work. He volunteered the information that over a period of months he was in the habit of wiping the accumulated sweat off the sweat band with his oily hands, and it was evident that the band had thus become saturated with oil. When he wore the hat subsequently, the oil caused an eruption on his forehead, although it had not done so at the time of his previous eruption. Oil was extracted from the sweat band with ether; the ether was then evaporated; and the patient had a positive reaction to the residual oil thus extracted from the sweat band.

Case 2.—This patient was employed as a painter and wore the typical painter's hat. The sweat band was a piece of paper impregnated with a sizing material, the nature of which could not be determined. After he had worn the hat some months, a typical crusted sweat band dermatitis ensued. There was a sharp outline of erythema, with scaling and hemorrhagic crusting encircling the head where the sweat band contacted the skin. A patch test to the paper gave positive results after 24 hours. The man was given treatment.

Case 3.—A worker in a tannery had suffered from a dermatitis from a tanning solution over a period of 10 years. During the last eight months it had been spreading. On examination, he showed a papular eruption of the arms, forearms, and hands, parts of his body in immediate contact with the solution, and similar dermatitis in areas about the knees where splashes of the chemical came in contact with his clothing above the high boots that he wore. He had a rash of the sweat band area, where he said he had been wiping the perspiration off of the sweat band.

Fig. 2 (case 2).—Typical case of sweat band dermatitis.

Summary and Conclusions

Chrome-tanned leathers are not used in sweat bands. This is the first report that trivalent chromium salts have been found in stockings. Basic chromic sulfate is a cause of dermatitis among sensitized persons. Sweat band dermatitis is not common. However, the diagnosis is simple, and

the cause may be the finishing material of synthetic fibers or of paper dissolved onto the skin by perspiration or it may be due to substances rubbed onto the sweat band by the hands.

520 Commonwealth Ave. (15).

References

1. Morris, G. E.: "Chrome" Dermatitis: Study of Chemistry of Shoe Leather with Particular Reference to Basic Chromic Sulfate, A. M. A. Arch. Dermat. **78:**612-618 (Nov.) 1958.

2. Morris, G. E.: Cross-Sensitization of Feet and Hands Due to Chrome-Tanned Leather Shoes and Gloves, New England J. Med. **257:**567 (Sept. 19) 1957.

3. Pirilä, V.: Sweat Band Dermatitis Due to Thiokol or Thioprene, Acta dermat.-venereol. **27:**287-298, 1947.

4. Straub, W.: Contact Dermatitis Following Wearing of New Hats, München med. Wchnschr. **94:**597-600 (March 28) 1952.

SHOCK AFTER ADMINISTRATION OF PROCHLORPERAZINE IN PATIENT WITH PHEOCHROMOCYTOMA

REPORT OF A CASE WITH SPONTANEOUS TUMOR DESTRUCTION

Irwin A. Brody, M.D., Durham, N. C.

Severe hypotension after administration of chlorpromazine is not common. Conventional doses may sometimes induce a moderate fall in blood pressure, but this is not usually sufficient to cause symptoms.[1] I have recently observed the sudden development of shock after administration of 10 mg. of prochlorperazine (Compazine) ethane disulfonate intramuscularly to a patient with a subsequently proved pheochromocytoma. This episode was followed by loss of function of the tumor. The purpose of this case report is to suggest that patients with pheochromocytomas may be unusually susceptible to the hypotensive effects of phenothiazine derivatives and that the occurrence of shock in this patient may have precipitated the degeneration of the tumor.

Report of a Case

An 18-year-old girl was admitted to Duke Hospital on July 25, 1958, for evaluation of recurrent abdominal pain. She had had headaches for six months, induced by exertion and relieved soon after lying down. Four weeks prior to admission she began to have recurrent attacks of generalized abdominal "pain" lasting about 30 minutes and often accompanied by vomiting. During the week preceding admission she had developed exertional dyspnea and orthopnea. Her health had previously been good. On physical examination her weight was 75 lb. (34 kg.); temperature, 101.4 F (38.6 C); pulse, 128 per minute; and blood pressure, 190/150 mm. Hg. The arterial pressure showed an orthostatic fall to 130/110 mm. Hg, and the pulse rate increased to 140. Her skin was pale and dry; the ocular fundi showed arteriolar spasm, venous compression, hemorrhages, and exudates. Neck veins were moderately distended. Examination of the heart revealed a loud split-second pulmonic sound; a harsh systolic murmur, accompanied by a thrill, was heard at the second left parasternal space. The liver was palpable just below the right costal margin. There was mild right costovertebral angle tenderness but no peripheral edema.

From the Department of Medicine, Duke University Medical Center.

Laboratory studies on the blood showed hemoglobin level, 9.4 Gm. per 100 cc.; hematocrit value, 36%; red blood cells, hypochromic; white blood cells, 15,960 per cubic millimeter. Urine showed a trace of protein, a trace of sugar, and was otherwise normal. The fasting blood sugar level was 121 mg. per 100 cc. and the nonprotein nitrogen level 27 mg. per 100 cc. Urine and blood cultures showed no growth. The electrocardiogram showed isolated T-wave negativity from V_2 to V_6. X-ray studies showed that the heart was at the upper limits of normal in size and the lungs were clear. An intravenous urogram demonstrated prompt excretion of the dye, but the right kidney was displaced downward.

Hospital Course.—The patient remained febrile but felt well until the fourth hospital day when she suddenly developed severe abdominal cramps and vomiting. Four hours later 10 mg. of prochlorperazine was administered intramuscularly to allay her symptoms. The patient's blood pressure fell within 10 minutes from 190/150 to 80/60 mm. Hg, and she had the clinical appearance of shock. She was placed immediately in the Trendelenburg position and levarterenol (Levophed) bitartrate was administered by intravenous drip. After five hours her blood pressure had stabilized at 120/80 mm. Hg and the levarterenol was discontinued. During the next 24 hours her blood pressure rose to a new level of 160/120 mm. Hg. The abdomen remained diffusely tender and distended without guarding and intestinal sounds were hypoactive.

By the seventh hospital day, about 96 hours after its onset, abdominal pain had subsided and the patient tolerated oral feedings. Thereafter she had only minor attacks of "pain." Her temperature gradually declined to normal by the 13th hospital day, and the intensity of her cardiac murmur diminished. Her blood pressure, which had remained at 160/120 mm. Hg during her period of severe pain, slowly decreased to 100/70 mm. Hg by the 16th hospital day. Intravenous administration of 5 mg. of phentolamine (Regitine) hydrochloride on the 11th hospital day produced a fall in blood pressure from 166/120 to 98/62 mm. Hg within 2 minutes, with a return to pretest levels within 10 minutes.

Urinary catechol amines were measured in the laboratory of Dr. M. Goodall by a bioassay utilizing cat's blood pressure and hen's rectal cecum.[2] The fluorometric method of Von Euler and Floding[3] was also used. The significantly elevated values of the 7th and 13th hospital days fell to normal by the 21st day (see table). Seventy-two hours elapsed between the

end of the levarterenol infusion and the beginning of the first urine collection. This time interval seems long enough to preclude the possibility that exogenous norepinephrine (noradrenalin) was being measured in the urine.[4]

After normotension had become established a hypertensive response could be provoked neither by the intravenous administration of 200 mg. of tetraethylammonium (Etamon) chloride or of 100 mcg. of histamine base nor by vigorous massage of the right flank.

*Urinary Catechol Determinations—Micrograms per 24 Hours**

	Fluorometric		Bioassay	
Hospital Day	Epinephrine	Norepinephrine	Epinephrine	Norepinephrine
7	...	2,330.6	...	...
13	65.5	270.4	54.8	1,112.4
21	15.3	36.5	13.2	44.1
27	...	...	...	...
(Tumor removed)				
41	17.9	29.5	3.2	31.8

* Average normal values [2]: epinephrine, 15.7; norepinephrine, 32.3

At laparotomy, on the 27th hospital day, a mass was found between the upper pole of the right kidney and the adrenal gland (see figure). This mass could be freed from the surrounding structures, but it was penetrated by the renal artery; consequently, the right kidney was excised after the renal artery was tied in removing the tumor. The adrenal gland was left intact. Throughout the procedure there was no significant change in blood pressure despite manipulation and removal of the tumor.

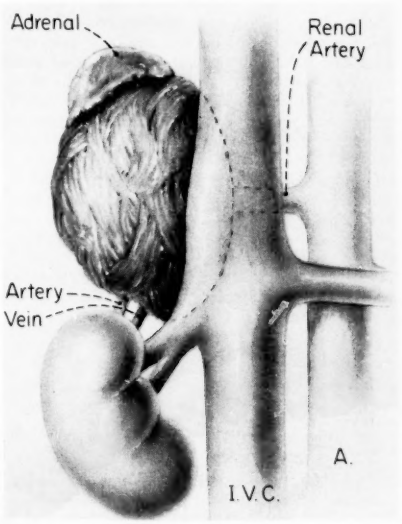
The patient's postoperative course was uneventful. She maintained a blood pressure of 110/80 mm. Hg and a pulse rate of 80 to 90 per minute, with orthostatic tachycardia. She felt entirely well on a return visit seven weeks after the operation, and her blood pressure was normal. Her eyegrounds showed complete resolution of the hemorrhages and exudates, and the arteriolar attenuation had disappeared.

Pathological Examination.—The gross specimen consisted of an encapsulated mass that weighed 5.4 oz. (153 Gm.) and measured 8 by 6.5 by 4 cm.; the capsule measured 7 mm. There was no connection with either the adrenal gland or the kidney. Cut section revealed that the tumor was yellowish brown, soft, and predominantly necrotic. Microscopic examination confirmed the impression of pheochromocytoma. There were no thrombi but the entire central mass was necrotic and had the appearance of an infarct. The infarcted area was organized from the periphery and among this fibrous tissue were small groups of chromaffin cells. Ghost-like cells in the necrotic center resembled these. The resected kidney appeared completely normal.

Comment

Phenothiazines and Shock.—The prompt development of shock in our patient after administration of prochlorperazine suggests that the drug precipitated her circulatory collapse. The pheochromocytoma may have predisposed her to this reaction or she may have been unusually sensitive to phenothiazines because of constitutional or other factors. An apparently normal individual rarely develops a marked fall in blood pressure in response to chlorpromazine.[1a] In our patient, however, another administration of 10 mg. of prochlorperazine intramuscularly seven weeks after the operation produced only a gradual, moderate decline in blood pressure without symptoms other than drowsiness, which made a constitutional basis for her severe hypotensive reaction appear unlikely. Hypertension itself does not seem to render a person more susceptible to shock induced by the phenothiazines. Stevenson and Sjoerdsma [5] studied the effect of intramuscular doses of 25 to 100 mg. of chlorpromazine in adults with benign essential hypertension and found no significant change in recumbent blood pressures.

On the other hand it seems that a patient with a pheochromocytoma, whose blood pressure is elevated by increased secretion of sympathetic amines, may be unusually sensitive to the hypotensive effects of the phenothiazines. There is much indirect evidence to support this view. Courvoisier and co-workers [6] found that chlorpromazine administered intravenously to dogs counteracted the pressor effect of infusions of norepinephrine and, to an even greater extent, of epinephrine (adrenalin). They stated that in large doses the effect of chlorpromazine resembled that of dibenzyl betachlorethylamine (Dibenamine) hydrochloride. Their animals were protected against a quantity of epinephrine equal to six times the lethal dose by the administration of 1 mg. of chlorpromazine per kilogram of body weight. Other studies have amply confirmed the adrenolytic properties of chlorpromazine.[7] Finkelstein and co-workers [8] showed that chlorpromazine in the fluid bathing an isolated heart muscle greatly reduced the positive inotropic action of epinephrine and norepinephrine.



Position of pheochromocytoma. Dotted lines show penetration by renal artery.

Although the adrenolytic effect of chlorpromazine might be the primary factor in causing a drop in the blood pressure of a patient with a tumor

producing sympathetic amines, this response might be intensified by some of the other pharmacological actions of chlorpromazine, including depression of the vasomotor center,[9] ganglionic blockade,[10] and direct peripheral vasodilatation.[11]

A survey of the literature reveals only one description of a case of hypertension associated with pheochromocytoma in which the effect of administration of a phenothiazine derivative is discussed. Lima and co-workers[12] reported a patient in Brazil with a pheochromocytoma to whom 25 mg. of chlorpromazine was given intramuscularly for sedation during a hypertensive crisis. The blood pressure fell from 280/160 to 70/30 mm. Hg and a vasopressor agent was required. During subsequent paroxysms the administration of chlorpromazine was invariably followed by a prompt hypotensive response. When therapy was maintained with prophylactic oral doses of chlorpromazine the hypertensive crises became less frequent and intense.

The symptomatology often associated with a hypertensive paroxysm may prompt the physician to administer one of the phenothiazine analogs, or the symptoms may be interpreted as an acute anxiety syndrome requiring a tranquilizer. The diagnosis of pheochromocytoma should be considered if a severe hypotensive response follows the administration of the drug.

Pheochromocytoma and Shock.—Another feature of interest in this case is the apparent association of the hypotensive reaction to the degeneration of the tumor. The development of shock in a patient with a pheochromocytoma before surgical excision has been described.[13] In many of these instances the tumor appeared degenerated at operation or autopsy, and the peripheral vascular collapse was attributed to the destruction of the tumor with abrupt cessation of pressor hormone output.[14] In the case here presented it seems possible that the sudden development of shock was responsible for initiating or accelerating infarction of the tumor and that generalized circulatory failure was thus the cause of tumor necrosis rather than its consequence.

It is conceivable that some degree of local vasoconstriction is present within a tumor containing large quantities of norepinephrine. Hence the tumor, with its great metabolic demand, may suffer chronically from a relative deficiency of blood supply. The cystic and necrotic areas frequently seen on pathological examination of actively functioning pheochromocytomas[15] may be a reflection of this state. The sudden superimposition of generalized circulatory failure may then precipitate massive infarction in the already ischemic tissue, leading to progressive loss of its highly specialized function.

The sequence of events here proposed has not been considered in the available case reports of shock occurring in patients with pheochromocytoma. It is conceivable that drugs were the real cause of shock in some of these patients or that their shock was similar to the circulatory failure observed in animals infused with large doses of epinephrine.[16] However the shock was produced, the necrosis of the tumor may have been merely a secondary phenomenon.

The evidence for tumor degeneration in our patient rests not only on the profound morphologic changes but also on the disappearance of hypertension, the negative responses to the provocative tests, the decline to normal of the urinary catechol amine levels, the absence of a hypertensive response during manipulation of the tumor at surgery, and finally on the stability of the blood pressure after removal of the tumor. The functioning pheochromocytoma had become converted into a physiologically inactive mass, rendering the patient asymptomatic before surgical intervention. A similar demonstration of loss of function of a pheochromocytoma was not found in the literature.

Summary

In a case of pheochromocytoma the administration of prochlorperazine was followed by generalized circulatory failure and then by loss of tumor function, documented by successive catechol amine determinations. Patients with pheochromocytomas may be extraordinarily sensitive to the phenothiazine drugs, and shock after their administration might point to the diagnosis of pheochromocytoma when the clinical picture is otherwise unclear. It is suggested that an episode of shock may play a significant role in promoting necrosis of a pheochromocytoma.

The catechol amine determinations were made by Dr. M. Goodall and the pathological examination by Dr. Bernard F. Fetter. The operation was performed by Dr. George J. D'Angelo.

References

1. (*a*) Rea, E. L.; Shea, J.; and Fazekas, J. F.: Hypotensive Action of Chlorpromazine, J. A. M. A. **156:**1249-1250 (Nov. 27) 1954. (*b*) Foster, C. A.; O'Mullane, E. J.; Gaskell, P.; and Churchill-Davidson, H. C.: Chlorpromazine: Study of Its Action on Circulation in Man, Lancet **2:**614-617 (Sept. 25) 1954.

2. Goodall, M.; Stone, C.; and Haynes, B. W.: Urinary Output of Adrenaline and Noradrenaline in Severe Thermal Burns, Ann. Surg. **145:**479-487 (April) 1957.

3. Von Euler, U. S., and Floding, L.: Fluorometric Estimation of Noradrenaline and Adrenaline in Urine, Acta physiol. scandinav. (supp. 118) **33:**57-62, 1955.

4. Von Euler, U. S., and Luft, R.: Noradrenaline Output in Urine After Infusion in Man, Brit. J. Pharmacol. **6:**286-288 (June) 1951.

5. Stevenson, T. D., and Sjoerdsma, A.: Blood Pressure in Patients with Hypertension Following Intramuscular Chlorpromazine, Proc. Soc. Exper. Biol. & Med. **86:**726-728 (Aug.-Sept.) 1954.

6. Courvoisier, S., and others: Propriétés pharmacodynamiques du chlorhydrate de chloro—3 (diméthylamino—3′ propyl)—10 Phénothiazine (4.560 R. P.): Etude expérimentale d'un nouveau corps utilisé dans l'anesthésie potentialisée et dans l'hibernation artificielle, Arch. internat. pharmacodynam. **92:**305-361 (Jan. 1) 1953.

7. Melville, K. I.: Observations on Adrenergic-Blocking and Antifibrillatory Actions of Chlorpromazine, Fed. Proc. **13:**386-387 (March) 1954. Reference 1*b*.

8. Finkelstein, M.; Spencer, W. A.; Hammer, C. S.; and Albert, S. N.: Effect of Chlorpromazine on Heart Muscle, and Its Influence on Inotropic Action of Three Sympathomimetic Amines, Fed. Proc. **13:**354 (March) 1954.

9. Hopkin, D. A. B.: Action of Chlorpromazine: Review of French Work, Lancet **1:**605-607 (March 19) 1955. Reference 1*b*.

10. Decourt, P.: Comment ont eté Conçues et réalisées les recherches qui ont abouti à l'introduction en thérapeutique de la chlorpromazine (4560 R. P.), Presse méd. **62:**541-543 (April 10) 1954. Reference 6.

11. Moyer, J. H., and others: Laboratory and Clinical Observations on Chlorpromazine (SKF–2601–A)—Hemodynamic and Toxicological Studies, Am. J. M. Sc. **227:**283-290 (March) 1954. References 1*b* and 6.

12. Lima, F. X. P.; Barros, N. M., Jr.; and Franca, H. H.: Feocromocitoma: considerações sôbre provas diagnosticas, com apresentação de um caso, Rev. paulista med. **50:**111-120 (Feb.) 1957.

13. Evans, V. L.: Suprarenal Tumor with Paroxysmal Hypertension: Case Report, J. Lab. & Clin. Med. **22:**1117-1120 (Aug.) 1937. Gilliland, I. C., and Daniel, O.: Phaeochromocytoma Presenting as Abdominal Emergency, Brit. M. J. **2:**275-277 (Aug. 4) 1951. Jelliffe, R. S.: Phaeochromocytoma Presenting as Cardiac and Abdominal Catastrophe, Brit. M. J. **2:**76-77 (July 12) 1952. Lehman, D. J., Jr., and Rosof, J.: Massive Hemorrhage into Adrenal Pheochromocytoma: Report of Case with Sudden Death, New England J. Med. **254:**474-476 (March 8) 1956.

14. Dybkaer, R., and Gjøl, N.: Phaeochromocytoma: Some Symptoms and Their Patho-Physiology, Acta. endocrinol. **26:**450-460 (Dec.) 1957.

15. Anderson, W. A. D.: Pathology, ed. 3, St. Louis, C. V. Mosby Company, 1957, p. 1041.

16. Freeman, N. E.; Freedman, H.; and Miller, C. C.: Production of Shock by Prolonged Continuous Injection of Adrenaline in Unanesthetized Dogs, Am. J. Physiol. **131:**545-553 (Jan.) 1941. Engel, F. L.; Mencher, W. H.; and Engel, G. L.: "Epinephrine Shock" as Manifestation of Pheochromocytoma of Adrenal Medulla: Report of Case with Successful Removal of Tumor, Am. J. M. Sc. **201:**649-661 (Nov.) 1942.

ACUTE ALLERGIC COLITIS PRESENTING THE CLINICAL PICTURE OF ACUTE APPENDICITIS

REPORT OF A CASE

Harold L. Karpman, M.D., Boston

This case report describes the effect of parenterally given epinephrine on colonic lesions in a case of acute colitis presenting the clinical picture of acute appendicitis.

A 47-year-old woman entered Beth Israel Hospital, Boston, on Sept. 1, 1955, with the chief complaint of abdominal pain of 24 hours' duration. The patient had been in good health until the evening before admission when, while sitting quietly, she noted the gradual onset of lower abdominal pain which became severe enough to cause fainting. The pain diminished somewhat but recurred; an analgesic was given subcutaneously for relief. The pain was described as cramping in nature with occasional severe exacerbations felt throughout the lower part of the abdomen. Between these exacerbations the patient noted a persistent ache in the lower part of the abdomen. She also experienced mild diarrhea. On the night prior to admission the patient had eaten lobster for dinner, as did several members of her family (no other members of the family were ill). Her history and a systemic review were completely negative except that the diagnosis of allergic rhinitis had been made in 1938.

Physical examination revealed a slightly obese, alert, cooperative female in no acute distress. Her pulse, respirations, and blood pressure were within normal limits, and the oral temperature was 99 F (37.2 C). Physical examination gave normal findings except for the presence of deep, right lower quadrant abdominal tenderness which could be demonstrated only with the patient in the right lateral decubitus position. Urinalysis revealed 1+ albuminuria. The white blood cell count was 19,600 per cubic millimeter. The diagnosis of acute appendicitis was made, and the patient was taken to the operating room.

At operation, performed by Dr. L. Hermansen, the cecum and transverse colon appeared normal, as did the sigmoid colon. However, a 12-cm. segment of the upper portion of the descending colon was involved in a bizarre reaction which ended abruptly at the junction of the descending colon and the signoid flexure; the entire intestinal wall was thickened and edematous but not discolored. Along the mesenteric borders of the intestine were numerous large bullae containing a clear fluid which was seen to extrude through the intestinal wall. The process resembled a local sensitivity phenomenon. Apparently the mesecolon and the adjacent peritoneum were not involved.

Biopsy was not deemed advisable. All fluid was aspirated from the bullae and 0.3 cc. of a 1:1,000 solution of epinephrine (Adrenalin) was administered parenterally with prompt partial regression of the process. Incidental appendectomy was performed, and the abdomen was closed in layers without drainage.

The postoperative course was benign, and the patient was discharged from the hospital on the sixth postoperative day. White blood cell counts prior to discharge from the hospital were normal and eosinophils were not present either in a differential smear or in an eosinophil count. Culture of the peritoneal fluid revealed no growth. The gross and microscopic examination of the appendix revealed a normal appendix. Routine scratch tests at the allergy clinic all gave negative results.

Assistant Resident in Medicine, Beth Israel Hospital. Dr. Karpman is now Instructor in Medicine, Department of Medicine (Cardiology), University of Southern California, Los Angeles.

Comment

Although mortality and morbidity from appendectomy have been reduced to extremely low levels,[1] there are many patients in whom it would be most desirable to avoid operation. In these patients one should use all available diagnostic techniques before scheduling even a "benign" surgical procedure. This report demonstrates the effect of epinephrine on acute bullous lesions of the serosal surface of the descending colon. As would be expected if the condition were allergic, these lesions regressed within minutes after the subcutaneous injection of epinephrine. It is, of course, impossible to correlate definitely the presence of these lesions with the clinical picture preoperatively, as it is also impossible to correlate the presence or absence of these lesions with the lack of symptoms postoperatively. One can say only that (1) the only intra-abdominal pathology found at laparotomy were these bullous lesions, (2) the appendix was normal histologically, (3) these lesions regressed rapidly after epinephrine was given parenterally, (4) the patient had no symptoms postoperatively, and (5) the patient had a definite allergic history in the past. The clinical syndrome apparently was due, therefore, to some vague allergic factor which produced the bullous lesions and which was counteracted by parenterally administered epinephrine.

Allergic symptoms of the gastrointestinal tract have been reviewed extensively by Withers,[2] Andresen,[3] and Miller.[4] Andresen[5] describes three types of colonic syndromes which apparently have an allergic component: a mild reaction commonly called "mucous colitis" or "irritable colon"; a more severe reaction which he terms "colon spasm" or "colitis"; and a very severe reaction simulating intestinal obstruction, acute inflammation, or perforation. Andresen notes that in the very acute phase of the severe reaction ephinephrine chloride, 1 cc. or less of a 1:1,000 solution, will afford immediate and almost miraculous relief of symptoms. Eusterman[6] describes a patient with recurrent painful gastrointestinal allergy in whom subcutaneous injection of epinephrine relieved symptoms within 20 minutes. Merrill,[7] too, notes that epinephrine often is useful in treating gastrointestinal allergy. He describes a patient with acute abdominal distress who received epinephrine to combat initial shock with a lessening of her abdominal symptoms; subsequent laparotomy revealed changes in the terminal ileum and cecum which supported a diagnosis of allergy.

Although epinephrine or ephedrine sulfate administered subcutaneously or atropine given orally may relax allergic spasm and aid in differential diagnosis, Ratner[8] cautions that surgical intervention may be imperative despite an allergic component: a too pronounced or prolonged allergic reaction may develop into a condition amenable only to operation. Therefore, even in the face of an allergic background, if the signs resemble appendicitis or intussusception, surgical intervention may be imperative.

Had epinephrine been administered prophylactically, it is quite possible that in the patient reported here the symptoms would have disappeared or at least abated in much the same manner as the intestinal lesions did. Therefore, one might suggest a therapeutic trial with parenterally given epinephrine in patients presenting a clinical picture of acute appendicitis where a history of allergic disorder is present and especially where it would be desirable to avoid operation. The epinephrine should be given immediately and the patient observed closely while preparations for operation are in progress; then, if operation is required it need not be delayed.

A note of caution regarding the use of epinephrine: Needless to say, epinephrine should not be used in anyone in whom a specific contraindication for its use exists, but, equally important, the administration of epinephrine should not lull the physician into a false sense of security even if the signs and symptoms abate. The patient should be watched closely for a reasonable period of time so that any evidence of persistence or recurrence of symptoms may be detected immediately and appropriate steps taken before serious complications occur.

Summary

In a patient, bullous lesions of the serosal surface of the descending colon (presumably allergic in nature) regressed after the parenteral administration of epinephrine. A preoperative diagnostic test with parenterally given epinephrine may be done in such patients. This test will be of help in the differentiation of acute appendicitis from acute allergic colitis, and it should also reduce the frequency of unnecessary laparotomies.

6221 Wilshire Blvd., Los Angeles 48.

References

1. McIver, M. A., and Broadaway, R. K.: Acute Appendicitis in Rural Community: Series III. 25-Year Summary, Ann. Surg. **145**:352-356 (April) 1957. Cantrell, J. R., and Stafford, E. S.: Diminishing Mortality from Appendicitis, ibid. **141**:749-758 (June) 1955.

2. Withers, O. R.: Gastrointestinal Allergy, Ann. Allergy **11**:637-680 (Sept.-Oct.) 1953.

3. Andresen, A. F. R.: Allergy of Gastrointestinal Tract, Rev. Gastroenterol. **18**:779-790 (Nov.) 1951.

4. Miller, M. M.: Gastro-intestinal Allergy, in Bockus, H. L.: Gastro-enterology, Philadelphia, W. B. Saunders Company, 1944, chap. 119.

5. Andresen, A. F. R.: Surgeon and Colonic Allergy, Am. J. Surg. **50**:281-287 (Nov.) 1940.

6. Eusterman, G. B.: Food Sensitivities Simulating Painful Abdominal Disease, Proc. Staff Meet. Mayo Clin. **5**:112-114, 1930.

7. Merrill, G. A.:: Gastro-intestinal Allergy, M. Times **70**:264-266 (Aug.) 1942.

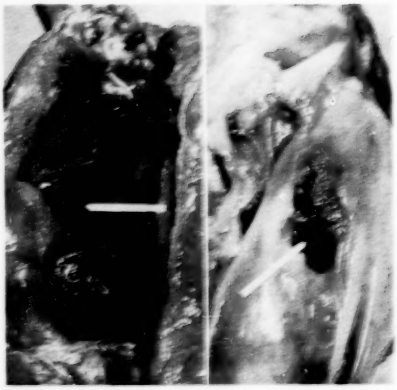
8. Ratner, B.: Abdominal Pain in Children due to Allergy, J. A. M. A. **127**:696-699 (March 24) 1945.

SPONTANEOUS RUPTURE OF AN ABDOMINAL AORTIC ANEURYSM INTO THE INFERIOR VENA CAVA

REPORT OF A CASE

Seymour M. Greenstone, M.D., Theodore Massell, M.D.
and
E. Craig Heringman, M.D., Sherman Oaks, Calif.

Although sporadic reports of arteriovenous fistulas between the aorta and inferior vena cava have been noted in the literature, these were the results of trauma, usually a gunshot wound. The spontaneous rupture of an abdominal aortic aneurysm into the inferior vena cava is a rare occurrence. Viar and Lombardo[1] reported in 1952 what they believed to be the first case. Their patient survived about six weeks after the development of such a spontaneous fistula, manifesting signs of severe progressive right heart failure, unresponsive to all medical therapy. Autopsy revealed a 13-cm. aortic aneurysm with a 1-cm. opening into the inferior vena cava.



Left, opening in arteriosclerotic aneurysm, revealing large fistula into inferior vena cava. *Right*, opening in inferior vena cava, revealing arteriovenous fistula.

More recently, Eiseman and Hughes[2] and Shumacker and Jontz[3] each described successful resection of an abdominal aortic aneurysm which had ruptured into the inferior vena cava and the replacement with a graft after closure of the caval defect. Both patients manifested severe cardiac failure, massive peripheral edema, widened pulse pressures, and pulsating abdominal masses with loud bruits. A case report describing some of the findings associated with this vascular catastrophe is given below.

A 69-year-old man, who had not been under prior medical care, was admitted on Nov. 25, 1956, with a six-hour history of severe abdominal pain followed by shock. Examination revealed an acutely ill elderly man with marked dyspnea and shallow respirations, pulse rate 120 per minute, and blood pressure 80/30 mm. Hg. The skin was cold and wet. Heart and lungs were within normal limits. A pulsating mass was present in the mid-abdomen and was associated with a to-and-fro murmur in this region and also along the vertebral spines posteriorly in the lumbar region. The pedal pulses were normal. Initial hemoglobin level was 15.1 Gm.%, his blood type was A positive. The initial impression was that a leaking abdominal aortic aneurysm was present. Emergency treatment consisted of nasally given oxygen and the infusion of 2 units of blood. The skin became warm and dry, but the rapid pulse and low blood pressure persisted. About three hours after admission he was taken to the operating room. During the induction of anesthesia he developed cardiac arrest. The left side of the chest was opened immediately through the fourth intercostal space, and cardiac massage was instituted. The heart developed ventricular fibrillation which was successfully defibrillated with the electric defibrillator. Cardiac massage was continued, but a satisfactory cardiac rhythm could not be reestablished.

Autopsy revealed a large fusiform aneurysm of the abdominal aorta arising about 2 cm. beyond the origin of the renal arteries. The aneurysm measured 10 cm. in diameter and it extended downward to the bifurcation (see figure). The aneurysm was partially filled with pale, yellow-tan, laminated thrombus measuring up to 3 cm. in thickness. The thrombotic layer was thinnest in the right posterior portion adjacent to the vena cava. In the center of this area the thrombus was eroded, and the attenuated aneurysm wall had ruptured through the wall of the inferior vena cava, producing an arteriovenous fistula which measured slightly more than 2 cm. in its greatest diameter. There was no evidence of rupture into the retroperitoneal space. The other regions of the aorta showed considerable arteriosclerotic changes in the ascending portion, arch, and major branches. The coronary arteries also showed extensive arteriosclerosis with calcification, but no serious impairment of the lumen. The remainder of the autopsy showed essentially normal findings.

Microscopic examination of the aorta in the region of the fistula revealed extensive infiltration of the wall of the aorta and the inferior vena cava with lymphocytes and plasma cells. The walls of both the aorta and the vena cava were markedly attenuated and showed fresh hemorrhage splitting the vessel walls.

Comment

The classic signs of an arteriovenous fistula with right heart failure—widened pulse pressure, peripheral edema, venous distention, enlarged liver—were not apparent in this case due to the rapidity of onset and the large diameter of the fistula. The to-and-fro murmur over the aneurysm and lumbar region was the only objective finding, and its significance was not recognized at the time. Holman[4] has stated that it is an experimentally observed fact

that, when a fistula is established between the aorta and vena cava 1-1.5 cm. in diameter, it is invariably fatal. It would appear that the smaller fistulas and those that develop gradually increase the cardiac return at a rate slow enough to allow initial compensation and, finally, the findings of right heart failure. Large fistulas that develop rapidly, such as is reported here, throw such a large burden on the heart that rapid cardiac failure or cardiac arrest is more likely.

Since the inferior vena cava is so closely applied to the aorta and since it is involved in the nonspecific inflammatory reaction that is so characteristic of arteriosclerotic aneurysms, it is interesting that more complications such as this have not been observed. The usual course is leakage into the retroperitoneal space with secondary rupture into the free peritoneal space. Rupture into the duodenum and other portions of the intestine is observed less frequently. With the progressively increasing number of aged persons in our population, more arteriosclerotic aneurysms will be encountered; the possibility of a fistula into the inferior vena cava should be considered in those persons who develop intractable right-sided cardiac failure.

Summary

In a patient with spontaneous rupture of an arteriosclerotic abdominal aortic aneurysm into the inferior vena cava, the fistula developed rapidly, was of large diameter, and precipitated cardiac arrest. Patients with smaller fistulas are more likely to develop intractable right heart failure and this should be considered in the differential diagnosis of this condition. Treatment should consist of resection of the aneurysm, replacement with a graft, and closure of the fistula into the inferior vena cava.

4911 Van Nuys Blvd. (Dr. Greenstone).

References

1. Viar, W. N., and Lombardo, T. A.: Abdominal Aortic Aneurysm with Rupture into Inferior Vena Cava, Circulation **5**:287-289 (Feb.) 1952.

2. Eiseman, B., and Hughes, R. H.: Repair of Abdominal Aortic Vena Cava Fistula Caused by Rupture of Atherosclerotic Aneurysm, Surgery **39**:498-504 (March) 1956.

3. Shumacher, H. B., and Jontz, J.: Rupture of Abdominal Aortic Aneurysm into Inferior Vena Cava: Successful Surgical Repair, Am. Surgeon **22**:1182-1185 (Dec.) 1956.

4. Holman, E.: Fundamental Principles Governing Care of Traumatic Arteriovenous Aneurysms, Angiology **5**:145-166 (June) 1954.

DIABETIC NEUROPATHY PRECIPITATED BY DIABETIC CONTROL WITH TOLBUTAMIDE

Max Ellenberg, M.D., New York

Tolbutamide (Orinase), a sulfonylurea derivative, is an orally given hypoglycemic agent which has recently been added to the therapy of diabetes mellitus. The introduction of any new drug into the therapeutic armamentarium necessarily requires careful observation to detect any toxic manifestations. This applies even more to tolbutamide, since, in addition to being a new drug, it is chemically related to the sulfonamides which have many known undesirable side-effects, the site and mode of action are not clearly defined, its use requires a prolonged period of administration, and it is a substitute for insulin, a known nontoxic agent which has been used safely and successfully for the past 25 years. On the other hand, it is equally important not to attribute to a drug undesirable but coincidental clinical phenomena that are inherent in the course of the disease under treatment and, hence, unrelated to any injurious effects of the medicament per se.

From the Department of Medicine, Mount Sinai Hospital.

To date, tolbutamide seems to have proved its clinical effectiveness and in many situations has facilitated the control of diabetes. So far, there have been remarkably few reactions and virtually none of any serious nature. Observed side-effects include relatively few hematological reactions, dermatological manifestations, gastrointestinal symptoms, and, more rarely, such ill-defined accompaniments as malaise, headache, weakness, and paresthesias.[1] A case of nephrosis during tolbutamide administration has been reported,[2] but its coincidental association has not been ruled out nor have any similar instances been recorded.

No previous reports of neurological complications have appeared in the literature. The following case reports are presented as instances of diabetic neuropathy after the use of tolbutamide to control the diabetes. It is the aim of this paper to indicate that the neuropathy is not a toxic manifestation of the drug but, rather, it has been precipitated or severely

exacerbated after the institution of good control and while the patients' diabetes remained under good control.

Report of Cases

Case 1.—On her first Mount Sinai Hospital admission, a 47-year-old woman had the chief complaint of pain in the right armpit, right upper part of the chest, and left lower extremity. The patient's diabetes was discovered five years before, when she visited a physician for weight-reducing instruction. At this time she was obese, weighing 230 lb. (104.3 kg.). Since then, she has lost 120 lb. (54.5 kg.)—100 lb. (45.4 kg.) up until six months before the present admission and another 20 lb. (9.1 kg.) since the onset of the present illness. During this five-year period she tested her urine about once a month, always detecting glycosuria but never having it treated. Six months prior to admission, in the course of a medical examination, glycosuria was again noted and hyperglycemia (blood sugar level 288 mg.%) was documented.

In view of the long-standing untreated diabetes and persistent weight loss, specific therapy in the form of tolbutamide was instituted. The patient received 1 Gm. a day. Fourteen days later she experienced the sudden onset of severe burning pain in the right scapular area radiating into the right axilla and the right breast. Two weeks after this, she noted tingling pain and paresthesias beginning in the left buttock which radiated down the lateral aspect of the left lower extremity to the midthigh. The pains were persistent, severe, and always worse at night and were relieved only by large amounts of narcotics, salicylates, and tranquilizers in combination. There was progressive weakness of both lower extremities, of the left more than of the right, with an accompanying sensation of numbness "as though my feet were no longer part of me." In association with these symptoms, the patient, although usually a jovial person, became depressed and developed anorexia. The patient was given 1,000 mcg. of vitamin B_{12} parenterally daily for three months. Because of the persistence of symptoms and their association with the administration of tolbutamide, the drug was withdrawn after four months. Nevertheless, the symptoms continued unabated.

Her history included total hysterectomy at the age of 23 years for fibroid tumors. The family history revealed the presence of diabetes in her mother, father, and two paternal aunts, one of whom had an amputation of an extremity for diabetic gangrene.

Physical examination revealed a middle-aged woman complaining of pain. Weight loss was evident. Examination of the fundi revealed pinpoint hemorrhages and exudates. Heart and lungs were normal; blood pressure was 130/80 mm. Hg; and the liver was palpable one fingerbreadth below the costal margin. Neurological examination revealed slow cautious gait, difficulty in arising from a squatting position, weakness of flexion at the hips and both knees, absent knee jerks and ankle jerks, hyperalgesia over the right upper thoracic segments T-7 to T-10 and on the left between S-1 and S-3, and decreased vibratory sensation over all the toes. The pupils were unequal and irregular and reacted poorly to light.

Laboratory investigation revealed a normal blood cell count, a trace of albumin in the urine, glycosuria of 1 to 4+, blood urea nitrogen level 13 mg.%, cholesterol level 345 mg.%, alkaline phosphatase level 6.8 King-Armstrong units, sedimentation rate 4 mm. per hour; blood Wassermann test result negative, and fasting blood sugar level 230 mg.%. X-ray of the chest and thoracolumbosacral spine showed normal findings. Lumbar puncture revealed clear fluid under normal pressure with normal manometric reading, cell count, and Wassermann and colloidal gold test results; the total protein level was elevated to 90 mg.%.

In view of the uncontrolled diabetes, the patient was started on tolbutamide therapy, 2 Gm. per day. This dosage was soon reduced to 1 Gm. a day and has been maintained uninterruptedly. While she was in the hospital, her symptoms started to abate and have progressively improved.

The symptoms, signs, elevated spinal fluid protein level, and course in this case were entirely compatible with diabetic neuropathy. Although tolbutamide was suspected as being a toxic agent for the radiculoneuropathy, the course was unaffected by withdrawal of the drug and later by reinstitution of the medication. In fact, the improvement started while she was receiving tolbutamide and continued progressively during maintenance of this therapy.

Case 2.—A 70-year-old woman had been carefully observed for the possible occurrence of diabetes for many years since her mother, each of her five sisters, and both brothers were known diabetics; two of them had died after amputation for diabetic gangrene. One month ago, she developed pruritus vulvae accompanied by mild polyuria and polydipsia but no weight loss. She quickly recognized the potential significance of these symptoms and instituted dietary restrictions but achieved little success. She therefore presented herself for more specific therapy. There were no complaints referable to the extremities, nor were there any sphincter disturbances. Her history included several attacks of cholelithiasis without jaundice.

On examination the pupils were normal, fundi showed no hemorrhages or exudates, heart and lungs were normal, blood pressure was 160/100 mm. Hg, the liver edge was palpable, and the peripheral pulses were palpable. Neurological examination, including tests of all reflexes and sensory modalities, showed entirely normal findings.

Laboratory examination revealed a normal blood cell count, blood urea nitrogen level 19 mg.%, cholesterol level 254 mg.%, blood Wassermann test result negative, electrocardiogram normal except for left axis deviation, fasting blood sugar level 184 mg.%, and urine normal except for a 2+ glycosuria.

The patient was given 2 Gm. of tolbutamide daily and a diet with 150 Gm. of carbohydrate, 80 Gm. of protein, and 80 Gm. of fat. Within one week she showed definite improvement: the fasting blood sugar level fell to 128 mg.% and the pruritus cleared considerably. The dosage of tolbutamide was reduced to 1 Gm. daily given before breakfast. Three weeks after starting treatment with tolbutamide and diet, the patient complained of numbness in the feet, more marked on the left than on the right and increased at night. The fasting blood sugar level at this time was 150 mg.%. Because of aglycosuria, the dosage of tolbutamide was lowered to 0.5 Gm. daily. However, the numbness continued to become increasingly severe. In addition, the patient now stated that her feet felt cold and "lifeless." At this time, the neurological examination revealed absent ankle jerks with depression of the knee jerk. There was stocking distribution of diminished light touch and vibratory sensations in both feet. Further observation of the patient revealed good control of the diabetes on the therapy with one tablet (0.5 Gm.) of tolbutamide daily. Although the drug was never withdrawn, the symptoms began to disappear two months after onset and were completely gone five months after institution of therapy.

The initial course of this patient seems to relate the neuropathy to the tolbutamide. However, the subsequent course, during which the neuropathy cleared despite continued medication, clearly puts this case into the category of neuropathy after institution of good diabetic control.

Case 3.—A 72-year-old man had developed diabetes 15 years before. His symptoms at that time consisted of polyuria, polydipsia, and weight loss. He was treated with diet and insulin until four years before the present illness, when his physician died. Since then there had been no observation of his diabetic status. Although he continued to take 15 units

of protamine zinc insulin daily, there was slow but steady, progressive weight loss of 20 lb. accompanied by polyuria, nocturia, and dryness of the mouth. He finally consulted a physician, who found uncontrolled diabetes and started the patient on tolbutamide therapy. The patient soon began to feel much better; polyuria, nocturia, and dryness of the mouth disappeared and he began to gain weight. However, four weeks after starting to take the drug, he developed a severe headache in the right temporofrontal area which was followed in five days by diplopia and inability to open his right eye.

Examination at this time revealed a complete ophthalmoplegia on the right. In addition, there was neuropathy involving the lower extremities manifested by absent knee jerks, absent ankle jerks, and absent vibratory sensation below the iliac crests. The blood pressure was 190/100 mm. Hg, urine showed 4+ albuminuria, the fundi did not reveal any hemorrhages or exudates, x-ray of the skull showed normal bones without evidence of injury or increased intracranial pressure, and the edrophonium (Tensilon) chloride test showed negative findings. The diabetes remained well controlled on 1.5 Gm. of tolbutamide, and this dosage was continued without interruption. With no other therapy, the oculomotor paralysis started to clear spontaneously in about one month and disappeared entirely over the course of the next three months.

This case illustrates the occurrence of extraocular muscle paralysis shortly after the institution of good diabetic control with tolbutamide and with complete disappearance of the involvement despite the continued use of the drug. The premonitory severe headache corresponding to the distribution of the first portion of the trigeminal nerve, followed by the nerve paralysis, the complete spontaneous resolution, and the absence of any other neurological disease is entirely compatible with the usual picture and course of extraocular nerve paralysis occurring in patients with diabetes.

Comment

The precipitation or exacerbation of diabetic neuropathy after the institution of control of diabetes has been previously recorded.[3] Recently, this sequence of events has been stressed with emphasis on the fact that the control of the diabetes is the factor involved.[4] Regardless of the means of achieving control, similar results have been noted. For example, although originally referred to in the literature as "insulin neuritis," the neuropathy may occur under comparable circumstances after the control of the diabetes by diet alone.[5] The arguments presented to establish this sequence of events with insulin include these statements: 1. The clinical picture, findings, and course were identical with all other forms of diabetic neuropathy. 2. The neurological syndrome cleared even though insulin administration was continued. 3. The same phenomena have been observed with diabetic control by diet.[4]

The same considerations apply to the case reports presented here. The neurological syndrome in each instance conformed to the accepted criteria of diabetic neuropathy, and the course was compatible with known experience. Above all, the manifestations cleared even though the administration of tolbutamide was maintained. In fact, in case 1, the tolbutamide therapy was reintroduced with no untoward effects; if the neuropathy were a toxic manifestation of the drug, then one would have expected this reintroduction to act as a "challenge" dose. Hence, it may be concluded that the tolbutamide is not the noxious agent but merely acts as the medium for control of the diabetes which in turn, in certain instances, leads to neuropathy. In the same vein, one may confidently predict that, with the forthcoming introduction of other orally given hypoglycemic agents, similar instances of neuropathy after control of diabetes will be encountered.

The etiology and mode of onset of diabetic neuropathy, along with many other factors, remain obscure.[6] It is possible that the relatively sudden change of the homeostasis may produce the equivalent of a stress phenomenon and thus precipitate the neuropathy. This suggestion stems from the observation that other stress phenomena, such as surgery, trauma, and infection, have been known to immediately precede the onset of neuropathy in the diabetic patient.

Summary

In three patients, the onset of diabetic neuropathy followed the institution of control of hyperglycemia and glycosuria with tolbutamide. Although this drug was suspected as being a toxic etiological agent, several factors absolve it of this role: The neuropathy in these circumstances was identical with the recognized forms of diabetic neuropathy, including symptoms, signs, and course; the neurological picture improved and symptoms disappeared despite the continued use of tolbutamide; and similar experiences have been reported with control of diabetes by insulin or dietary restrictions. Thus, tolbutamide is not the noxious agent but acts as the medium for control of the diabetes which, in certain instances, leads to neuropathy.

45 E. 66th St. (21).

References

1. Mehnert, H.; Camerini-Dávalos, R.; and Marble, A.: Results of Long-term Use of Tolbutamide (Orinase) in Diabetes Mellitus, J. A. M. A. **167:**818-827 (June 14) 1958. Hurwitz, D., and McCuistion, A. C.: Tolbutamide: Double-Blind Study of Its Effect in Diabetes, New England J. Med. **257:**931-933 (Nov. 7) 1957.

2. Schnall, C., and Wiener, J. S.: Nephrosis Occurring During Tolbutamide Administration, J. A. M. A. **167:**214-215 (May 10) 1958.

3. Jordan, W. R.: Neuritic Manifestations in Diabetes Mellitus, Arch. Int. Med. **57:**307-366 (Feb.) 1936. Rudy, A., and Epstein, S. H.: Review of 100 Cases of "Diabetic Neuropathy" Followed from 1 to 10 Years, J. Clin. Endocrinol. **5:**92-98 (Feb.) 1945.

4. Ellenberg, M.: Diabetic Neuropathy Precipitating After Institution of Diabetic Control, Am. J. M. Sc. **236:**466-471 (Oct.) 1958.

5. Rundles, R. W.: Diabetic Neuropathy: General Review with Report of 125 Cases, Medicine **24:**111-160 (May) 1945. Rudy, A.: Diabetic Neuropathy, New England J. Med. **233:**684-689 (Dec. 6) 1945. Reference 4.

6. Ellenberg, M.: Diabetic Neuropathy: Pitfalls in Diagnosis, A. M. A. Arch. Int. Med. **100:**906-915 (Dec.) 1957.

THE JOURNAL
OF THE AMERICAN MEDICAL ASSOCIATION

Editor . . . . . JOHNSON F. HAMMOND, M.D.
Assistant Editors . . . . . WAYNE G. BRANDSTADT, M.D.
FREDERIC T. JUNG, M.D.
Assistant to the Editor . . . . . MILTON GOLIN
Editor for Medical Literature Abstracts . GEORGE HALPERIN, M.D.
News Editor . . . . . CHARLES CHAPMAN
Feature Writer . . . . . RICHARD P. PRATT

•

Subscription price . Fifteen dollars per annum in advance
Cable Address . . . . . "Medic, Chicago"

SPONTANEOUS REGRESSION OF MALIGNANT DISEASE

GUEST EDITORIAL

Tilden C. Everson, M.D.
and
Warren H. Cole, M.D.

FOR DECADES the reported disappearance or regression of malignant tumors, without significant therapy to explain it, has intrigued the profession, and has given rise to controversy as to whether or not the phenomenon actually exists. Spontaneous regression of cancer may be defined as the partial or complete disappearance of a malignant tumor in the absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant influence on the growth of neoplastic disease. Indeed, spontaneous regression is a somewhat inaccurate term for this phenomenon because any change in the growth pattern of malignant tissue must have a biological explanation.

Efforts to find an explanation of this phenomenon have been thwarted by the fact that, fortunately, only a small fraction of patients with malignant disease go untreated. Thus, spontaneous regression of cancer has been mainly reported in patients in whom the cancer was beyond the scope of cure by the accepted techniques of surgery and/or radiation.

To help find an answer to this phenomenon we have studied the hundreds of cases which have been reported in the world literature since 1900 as examples of spontaneous regression of cancer, and have solicited unpublished reports of cases from our medical and surgical colleagues. The majority of the published cases have been too poorly documented to be considered as valid examples. Most frequently microscopic diagnosis of the malignancy has been lacking.

Of the entire group of cases reported, or made available by our medical friends, we have collected 112 cases which appear to have adequate documentation (including histological diagnosis of the malignancy) to be acceptable as probable examples of spontaneous regression of cancer. This phenomenon was reported most commonly in neuroblastoma (25 cases), choriocarcinoma (14 cases), carcinoma of the kidney (11 cases), malignant melanoma (10 cases), soft-tissue sarcoma (9 cases), and carcinoma of the bladder (7 cases). Spontaneous regression was more rarely reported in the commonly occurring cancers such as carcinoma of the breast (5 cases), carcinoma of the stomach (3 cases), cancer of the colon and rectum (3 cases), and carcinoma of the uterus (3 cases).

The regressions in these collected cases have been divided into two general types: (1) regression of the primary tumor and (2) regression of metastases. In some of the patients with regression of metastases, microscopic confirmation of the metastases is lacking, although in every case microscopic diagnosis of the primary lesion is available. Clinical and x-ray examinations have been the basis of diagnosis of the unconfirmed metastases.

In looking for an explanation of the spontaneous regression of cancer the first consideration is that the original histological diagnosis of cancer may have been incorrect. However, in 67 of the 112 cases tissue slides or photomicrographs have been available for review. Clinical and experimental knowledge indicates the probable importance of endocrine factors in at least some spontaneous regressions of choriocarcinoma, carcinoma of the kidney, malignant melanoma, malignant teratoma, carcinoma of the ovary, and carcinoma of the breast. An impairment of the blood supply appears to be a possible explanation, particularly in the neuroblastomas, since some of these were partially removed at operation and the remaining portion traumatized by the attempt to remove it. Most of the patients with regression of a bladder tumor had had diversion of the urine by transplantation of the ureters. In these cases it would seem that a carcinogenic agent in the urine was necessary for the development and continued growth of the tumor. Fever and/or infection may be implicated as the cause of spontaneous regression in several cases.

Although our study has led us to the conclusion that spontaneous regression of malignant tumors may occur on very rare occasions, we are unable to offer a figure as to its true incidence. This inability to establish a figure of incidence is partly related to the fact that we have no way of knowing how many patients are alive or dead without treatment. We believe the phenomenon is very rare, but it is barely possible that a few of the good results after therapy are related to spontaneous regression.

From the Department of Surgery, University of Illinois College of Medicine, Chicago.

The probability of spontaneous regression occurring in any single case of cancer is so extremely small, however, that any patient would be most foolish to reject orthodox methods of treatment in the hope that his cancer would regress spontaneously.

Evidence of the occurrence of spontaneous regression of cancer supports the concept of biological control of cancer and reinforces the hope that more satisfactory methods of treating cancer than surgery and/or radiation may be found in future years. Also, the occurrence of spontaneous regression of cancer demonstrates the need for caution in the assessment of the value of chemotherapeutic and unorthodox therapeutic measures in isolated "cures" of cancer.

The remote possibility of spontaneous regression of cancer may be of some psychotherapeutic value in offering hope to patients and relatives of patients with "incurable" cancer. Often, indeed, the mere thought that regression might possibly take place changes their attitude from that of complete despair to that of hopeful toleration. The profession should use knowledge of this phenomenon, rare as it is, in an endeavor to comfort the patient and his relatives in the trying days of terminal cancer. With proper precaution the physician can do this without being guilty of offering false hopes.

NATIONAL CANCER INSTITUTE STUDY OF KREBIOZEN

The American Cancer Society statement dated March 9, 1959, which appears in this issue of THE JOURNAL, page 1790, urged that the Krebiozen Research Foundation accept the proposal of the National Cancer Institute of the U. S. Public Health Service to test the controversial cancer substance, Krebiozen, in "a manner acceptable to the scientific community." This statement reviews the history of Krebiozen; it clarifies the issues and presents the society's position regarding it.

Since the Krebiozen Research Foundation, its spokesmen, and advocates have "long claimed they have a useful tool against cancer," the American Cancer Society indicated that "it is then their clear duty to thousands of cancer patients to cooperate with the National Cancer Institute or any group of competent, objective scientists in an objective test of the drug." Furthermore, the society indicated that the "delays" which have recently been given so much publicity by the Krebiozen Foundation "are now clearly the responsibility" of that foundation.

The American Medical Association concurs with the American Cancer Society that the prolonged and continued agitation associated with the Krebiozen controversy has a disturbing and unsettling effect on many cancer patients as well as on their relatives and friends, who are bewildered and wonder whether or not the many extraordinary claims made for Krebiozen are actually true.

In 1952 the Committee on Research of the Council on Pharmacy and Chemistry of the American Medical Association published a lengthy report which did not support the contentions of the promoters of the substance at that time. A Committee on Cancer Diagnosis and Therapy of the National Research Council came to essentially the same conclusions. A committee of six distinguished physicians from several medical schools, headed by Dr. Warren H. Cole, reviewed 500 cases of cancer treated with "Krebiozen" and came up with a number of conclusions, including: "Ignorance of the material interferes with a sound evaluation of its therapeutic effectiveness. . . . no acceptable evidence that any malignant tumor had been cured by Krebiozen. . . . no evidence of prolongation of life. . . . no histological evidence that Krebiozen produced degenerative or regressive changes in tumor cells."

Even though no convincing scientific evidence has been presented during the intervening eight years since the substance was announced, the American Medical Association is currently of the opinion that it is in the public interest that this controversy be terminated. It is in complete agreement with the American Cancer Society that this can be accomplished only through the medium of a thoroughly objective study such as that which the National Cancer Institute has indicated it is prepared to undertake.

Sound research in medicine calls for precise chemical and biological studies, for extensive work on animals, for sustained work in recognized laboratory and clinics, for prior publication in technical journals, for criticism, and for the encouragement of like technical studies elsewhere. These are the proper channels for scientific evaluation of any drug or substance and there is no logical reason why they cannot be followed with Krebiozen.

The American Medical Association, along with the American Cancer Society and, it is believed, with the concurrence of all other scientific organizations expresses the hope that the Krebiozen Research Foundation will recognize the integrity of the National Cancer Institute of the U. S. Public Health Service and proceed to cooperate with this agency that is endeavoring to scientifically evaluate actual and alleged cancer therapy. The American Medical Association believes that in this way the public interest would best be served.

The Krebiozen Research Foundation should desist in its demands for an evaluation of the efficacy of Krebiozen dictated according to its own terms, rules, and procedures which are contrary to the soundly established scientific approaches utilized in the evaluation of substances alleged to be of therapeutic value in malignant disease.

If the representations of the owners and promoters of Krebiozen possess any degree of validity there is nothing to lose and much to gain from such an objective analysis. Failure to accede to such an objective evaluation can be interpreted as an expression of fear or doubt concerning the results of removal of the secrecy which has persistently shrouded Krebiozen through the eight years of its promotion.

ORGANIZATION SECTION

STATEMENT TO SENATE ARMED SERVICES COMMITTEE ON H. R. 2260

March 2, 1959

The Honorable Richard B. Russell, Chairman
Committee on Armed Services
U. S. Senate
Washington 25, D. C.

Dear Chairman Russell:

The purpose of this letter is to submit for the consideration of the Committee on Armed Services the position of the American Medical Association on H. R. 2260, 86th Congress, a bill, which, in part, would extend until July 1, 1963, the induction provisions of the Universal Military Training and Service Act.

With respect to the extension of the special provisions of this Act applicable to medical, dental, or allied specialists, the American Medical Association wishes to reaffirm its position which was outlined in testimony presented in 1957, on the bill which subsequently was enacted as Public Law 85-62, approved June 27, 1957. At that time, the Association testified that, ". . . if the demands for the defense and security of our nation are such that, in the opinion of Congress, it is necessary to have a draft act to maintain the strength of our Armed Forces, then the extension of the present legislation would be one method to insure sufficient physicians for the military services."

The Association also recommended retention of the provisions of the law relating to the national, state and local committees which advise the Selective Service System in regard to the selection of medical, dental and allied specialists required by the services. These advisory committees consider, among other factors, the needs of the civilian population in the communities from which these physicians would be taken. The Association is pleased that this provision is a part of the current law.

In regard to specialist categories, the Association recommends, as it did previously in May, 1957, that the word "other" should be substituted for the word "allied" in this section of the law. This would authorize a selective call for other specialists, such as engineers, physicists, other scientists, et cetera, which might be needed by the military forces. Presently, the law provides only for the selective callup of medical, dental, or "allied" specialists.

The Association believes that physicians should be registered and classified in the same manner as other citizens in the same age group, deferred for educational purposes in the same manner as other registrants and called to active duty or inducted under the same general provisions as other registrants deferred for educational purposes.

It is noted that the pending bill proposes a four year rather than a two year extension of the Universal Military Training and Service Act. We believe the additional two year extension of time should be fully explained and justified to the Committee. We believe that this justification is necessary because scientific and technological advances have resulted in rapidly changing concepts of military manpower requirements. Consequently, there have resulted, directly or indirectly, current and projected reductions in the strength of the Armed Forces. It is conceivable that future manpower requirements may be subject to further downward revisions. A two year extension of the law would permit a timely review of military manpower requirements in light of pertinent changes in the then current military situations. The Association believes that this would be particularly desirable with respect to the callup of medical and allied specialists because of the increasing demands and requirements of the civilian population for the nation's medical and health resources.

As you know from our previous appearances before your Committee, the Association has had a keen and sustained interest in military medicine for many years. Through the Surgeons General of the military services, we have maintained a friendly and close working arrangement in the consideration and advancement of military medical affairs. We feel that the health of the nation requires a careful correlation of military and civilian medicine. In furtherance of this objective, the Association, working with the military services, has attempted to insure improvement in the utilization of medical manpower by the Armed Services and a strengthening of the career incentive program for medical officers.

On behalf of the American Medical Association, I would like to thank you for this opportunity to present our views on H. R. 2260 and to assure your Committee of our willingness to continue our assistance in providing the members of the military services with the finest medical care.

Yours sincerely,
F. J. L. Blasingame, M.D.
Executive Vice-President

STATEMENT OF THE AMERICAN MEDICAL ASSOCIATION ON S. J. RES. 41, 86th CONGRESS

THE INTERNATIONAL HEALTH AND MEDICAL RESEARCH ACT OF 1959
SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE
BY GUNNAR GUNDERSEN, M.D.
FEB. 25, 1959

Mr. Chairman and Members of the Committee:

I am Dr. Gunnar Gundersen, a practicing physician from LaCrosse, Wisconsin. I currently am serving as the President of the American Medical Association, on whose behalf this statement is presented.

In addition to my position with the A. M. A., I am a member of the Council of the World Medical Association, an organization of 53 national medical associations comprising a membership of more than a half million physicians.

With your permission, Mr. Chairman, I should like to discuss briefly the interest and activities of the American Medical Association in connection with international health, medical care and medical education, and the philosophy and position of the A. M. A. with respect to the subject resolution which would establish a National Advisory Council for International Medical Research.

For many years the American Medical Association has played an active and far-reaching role in the international health field, because of its belief that physicians on every continent are dedicated to the assistance of all people regardless of race, color, creed, or social class in attaining the highest possible level of health.

Here briefly are a few of the ways in which the A. M. A. has acted specifically upon this belief:

1. The Association helped to organize and support the World Medical Association in 1948. We also approved and encouraged a United States Committee to aid the World Medical Association financially. This committee has provided, and is furnishing, funds to help finance the W. M. A. Secretariat, the publication of the *World Medical Journal*, and specific scientific investigations.

2. An A. M. A. representative has served with the U. S. delegation to the Assembly of the World Health Organization, a subsidiary of the United Nations representing governments in the field of medicine.

3. THE JOURNAL of the American Medical Association is promoted in foreign countries, and now serves as an "up-to-the-minute" medical textbook for approximately 10,000 subscribers overseas. It can be found in every recognized medical library in the world.

4. Likewise, our nine specialty journals reach thousands of physicians outside the United States, providing them with the latest medical information on subjects relating to their specialties.

5. The A. M. A. has established, developed, and maintained the valuable "Standard Nomenclature of Disease and Operations," the only international publication of its type.

6. The A. M. A. library staff compiles the "Quarterly Cumulative Index Medicus," a publication providing pertinent information on medical periodicals, literature, and books. Currently there are more than 1,300 foreign subscribers.

7. Other A. M. A. publications which have wide appeal among physicians abroad include "New and Non-Official Remedies" and "Useful Drugs." These publications provide physicians with information on the actions, uses, limitations, and dosages of new drugs.

8. A. M. A. medical films are loaned to medical societies all over the world. In the past 10 years the A. M. A. has received approximately 775 unsolicited requests from 70 countries for medical films. While it was impossible to fill all the requests, hundreds of films have been provided on a loan basis.

In addition, the A. M. A. has cooperated with many national medical societies in arranging film programs. This year a special film program has been prepared for the Japan Medical Society.

9. The A. M. A. has been vitally interested in the training, in American hospitals, of physicians educated abroad and is a participating member of an evaluation service for foreign medical graduates. In 1957-1958 a total of 7,622 physicians from 90 countries were trained in American hospitals as interns or residents. (Open Doors, 1958, prepared by Institute of International Education.)

10. This year the American Medical Association, along with the Association of American Medical Colleges, will play host to the Second World Conference on Medical Education in Chicago (Aug. 30-Sept. 4). Our Association again is giving its wholehearted cooperation to this conference which is expected to draw more than 1,500 persons from all parts of the world.

I am sure all of you are familiar with the dramatic television production, "MD International," sponsored by Smith, Kline & French Laboratories and the American Medical Association. The film was inspired by President Eisenhower's People to People speech, in which he said that one of the best roads to international understanding was through constructive personal contact among individuals of all nations.

"MD International" was premiered at the 1957 Clinical Session of the American Medical Association in Philadelphia. In introducing it, Dr. David B. Allman, who was then President of the Association, said:

"MD International is a warm and inspiring account of the activities of American doctors who chose to practice in the far corners of the world.

These physicians, and many like them, act as our unofficial medical diplomats. Not only do they carry modern medicine to people in remote areas but they also—through their daily lives and through dedication to their patients—help spread good will and understanding.

"The contribution of these doctors of medicine is a great steppingstone on the path to peace."

I have mentioned some of the ways in which the American Medical Association is working, with others around the world, to promote better health, medical care, medical facilities, and medical education.

Our Association feels that medicine has no geographical boundaries, for it truly is an international science for the benefit of everyone. Furthermore, we believe that only through coordinated effort can physicians throughout the world bring to their people the maximal health benefits that modern medicine can provide.

Today more than ever before medical men all over the world are interdependent. Consequently, physicians in America are interested not only in exporting new developments in the art and science of medicine but also we are equally anxious to import new techniques and discoveries by our colleagues in other countries. World-wide progress in medicine can continue in the future only through the free exchange of ideas between medical scientists in all countries.

Last June at the presidential inaugural ceremony of the American Medical Association I titled my address "Physicians to the World." Allow me to quote a few of the concluding lines from that address:

"In medical science there are no secrets, no iron curtains, no cold war. To physicians everywhere, atomic energy means a new way of fighting disease, not a new way of conquering the world. Medicine exists to save life, not destroy it."

Since medicine speaks a common language around the world we can combat physical and mental suffering with more medical knowledge and research. Obviously, there are enormous potentials for health and good living which are still unrealized both in the United States and in all other countries. In addition, there is a growing recognition that medicine, with its resources and influence fully mobilized, can perhaps do more for world peace than the billions of dollars being poured into armaments. There is a mounting conviction that the time has come when medical statesmanship must be used to augment the methods of political diplomacy.

I believe that Senate Joint Resolution 41, 86th Congress, will provide an important way in which the United States can contribute to the health and well-being of our own citizenry and of all the peoples of the world.

We in medicine have long recognized that native intuition and the ability to apply scientific methods of research are gifts which are not confined to people in only a few nations of the world. Men and women of science in all countries can contribute substantially to the expanding horizons of medical knowledge.

The establishment of the National Advisory Council for International Medical Research and the National Institute for International Medical Research can provide a vital vehicle for implementing and assembling our existing and potential forces of medical science.

After careful study of Senate Joint Resolution 41, I have a few other points that this committee may want to consider:

1. I believe that the World Medical Association is another of the already existing, tested means for international cooperation in matters relating to health. Therefore, it should be included along with the World Health Organization, the Pan American Sanitary Bureau, and the United Nations International Children's Fund, as international groups to cooperate with.

2. I agree basically with the manner in which the Council is to be appointed—"by the Secretary without regard to civil service laws." However, it would be my suggestion that the Secretary of the Department of Health, Education, and Welfare rely heavily on the surgeon general of the Public Health Service in making the appointments because of the professional character of the Council.

3. Naturally due care must be taken in supporting researchers in foreign countries because of the possible salary differential. While the financial grants to foreign researchers must be adequate—perhaps even attractive—the secretary and his advisers must see that the program does not adversely affect medical care and scientific research in foreign countries.

4. Generally, the Senate Joint Resolution deals with research, investigations, and experiments by individuals, universities, hospitals, laboratories, or other public agencies or institutions. However, there is a reference to grants for the improvement or alteration of facilities needed for medical research and research training. I believe that the

program should be one of research and not a research construction program. Perhaps it would aid and guide the secretary, the surgeon general, and the council if some general qualifications or limitations on grants for the improvement or alteration of facilities were added.

5. Finally, I believe that the greatest care should be exercised in setting up the research grants and research programs. Because of the vast amount of research being conducted today, all proposed projects must be scrutinized carefully.

Last December in my report to the House of Delegates of the American Medical Association, I stated that medicine should offer leadership and imagination on the international scene. At that time proposals for an International Medical Year were being made. In support of such a project I said that the American Medical Association should offer maximum help and leadership as a contribution to world understanding.

In furtherance of this belief, the American Medical Association offers its full support and assistance in the establishment of the National Advisory Council for International Medical Research and the National Institute for International Medical Research, proposed by S. J. Res. 41. We believe that the promotion of international health through research is one of our best means of promoting international cooperation and understanding. Whatever we do to promote good health also will promote peace in the world.

Thank you, Mr. Chairman and members of the committee, for giving me this opportunity to testify here today.

COUNCIL ON MEDICAL SERVICE

CHRONIC ILLNESS INFORMATION CENTERS

In most cities a wide variety of services and facilities are available for long-term patient care. These may range from a chronic disease hospital or an organized home-care program to nursing homes or visiting nurse and homemaker services. Whatever their function or sponsorship, they are too frequently either unknown to or overlooked by physicians having patients with illnesses that do not require general hospital care.

A comparatively recent approach to the better utilization of such services and facilities has been the establishment of what are being variously termed "central services for the chronically ill," "chronic illness information centers," or the like. These agencies provide information and referral services to physicians or to patients seeking the proper facility, conduct fact-finding studies on needs and resources for care, stimulate and coordinate planning, and, in general, serve as community clearing-houses on chronic illness planning and activity. The first such service was established in Chicago in 1944. Four others have been organized along similar lines at later dates in San Francisco, Milwaukee, Cleveland, and Essex County, N. J.

Although these agencies differ in the emphasis placed on various facets of their operation, all are organized to a greater or lesser degree around the following general functions: (1) to collect and maintain current information on all available community facilities and agencies offering service to the chronically ill or aged and to provide referral services to individual patients or other persons seeking the appropriate service; (2) to provide consultation and guidance to the operators of nursing homes, homes for the aged, and other long-term facilities in regard to standards of care, operating methods, and costs; (3) to conduct or participate in fact-finding research into the prevalence of long-term illness or disability in the community, the important unmet needs for care, and the additional facilities and services necessary; and (4) to initiate, stimulate, and coordinate community planning to meet these needs, through contacts and conferences with appropriate groups and individuals and through public education, both professional and lay.

The Council on Medical Service has undertaken an expanded program of research, education, and implementation in the various problem areas of aging and long-term illness. Because of the important role such information and referral centers play in coordinating care for these two groups, it was decided to gather information on their organization and operation, the types and needs of persons they serve, the special programs and projects undertaken, and the major problems encountered in serving the aged and chronically ill.

Reports on the chronic illness centers in Chicago and Milwaukee follow. Reports on the other three centers will appear in subsequent issues of THE JOURNAL. It is believed that the data obtained will be of interest to physicians, medical societies, and other groups and individuals who are either involved in the care of these types of patients or concerned with the over-all problems of aging and long-term illness.

CENTRAL SERVICE FOR THE CHRONICALLY ILL OF THE INSTITUTE OF MEDICINE OF CHICAGO

The Central Service for the Chronically Ill of the Institute of Medicine of Chicago began operation in January, 1944, with the financial sponsorship of the Community Fund. Its inception had been preceded by more than 10 years of increasing concern and tentative planning for the growing number of chronically ill in Chicago, on the part of various committees of the Welfare Council, the Institute of Medicine, and other medical, public health and welfare agencies. In the fall of 1942, plans were crystallized when the Welfare Council Committee on Chronic and Convalescent Care recommended that a special agency be established to devote full-time attention to the needs of the chronically ill and the community services necessary to meet these needs. It was intended that the agency would serve as a central point for assembling comprehensive and current data on facilities for the chronically ill in Chicago and on the improvements and additional facilities needed, would concentrate the interest of medical and welfare groups and the general public on these unmet needs, and would formulate specific proposals for improvement of care. It would also provide information on the best services available to patients or other persons seeking care.

In the belief that the work should be under medical auspices, the welfare council had approached the Institute of Medicine during the planning stages with a suggestion that the institute sponsor the project and had added representatives of the institute to the planning committee. Funds for the work became available before final arrangements for sponsorship had been completed, and, to avoid delay, the project was established under the auspices of the welfare council, with institute representation on the governing committee. It operated in this way for the first four months of its existence. On May 1, 1944, it was formally transferred to sponsorship of the Institute of Medicine with the same governing committee, including representatives of the welfare council, and with the same staff and program. A representative of the welfare council continues to serve on the governing board of the Central Service for the Chronically Ill, and, in this and other ways, efforts are made to coordinate the work of the two organizations.

Early in the work of the central service the purposes and program were broadened to include activities directed toward prevention and control of long term illness, as well as toward the improvement of care. These revised purposes, which have directed the central service's activity to the present, are (1) the determining of the important problems of chronic illness in the community through fact-finding studies and accumulation of information from other sources on the number of chronically ill persons, the nature of their disabilities, the services required to meet their needs, the kinds of agencies and institutions best able to provide the necessary services, the part each should play in the total community program, and the ways in which the various personnel, agencies, and institutions should be integrated with each other in providing service; (2) the development of a comprehensive plan outlining the additional services and facilities required in the community and promotion of the development of these facilities through education, consultation with persons and organizations planning new facilities, and other methods; (3) the promotion of the most efficient use of existing services by providing information, counseling, and referral to patients and their families, physicians, health and social agencies, and others seeking suitable facilities for care; (4) the furthering of the effective programs for the prevention and control of long-term illness by encouraging additional effort in this field and by coordinating the facilities and services for care with those whose primary activities are related to prevention; and (5) the fostering of good standards of care and rehabilitation for the chronically ill and disabled at home and in all types of institutions by developing and making available to the personnel and institutions involved specific descriptive and standard-setting material on the quantity, quality, and reasonable costs of services and supplies necessary for adequate care, and by providing consultation in problems of management and administration to these institutions and facilities.

Although the information and counseling service has been operated continuously since the central service was established, a major part of the organization's work up until 1954 revolved around the collection of community-wide data on the needs of the chronically ill, the formulation of standards, and the development and promotion of a community plan to meet the needs. By 1954, the major community problems of chronic illness had been identified and clarified. Information had been collected on the types and extent of additional services and facilities needed, the advantages and disadvantages of various methods of organizing these services, costs, and possibilities for financing; the comprehensive community plan had been developed. This brought to a close the temporary purposes for which the center had been established.

The need continued, however, for referral and counseling services to individual patients and for guidance and consultation to facilities caring for these patients, particularly private nursing homes. In response to considerable community pressure,

and with financial help from the Chicago Medical Society, Community Fund, Chicago Community Trust, Illinois Division of the American Cancer Society, Chicago Heart Association, and some private foundations, the central service was established on a permanent basis in the Institute of Medicine to continue these two functions. It has been operating on this basis up to the present.

Organization and Operation

The central service now occupies an office in the John Crerar Library Building adjacent to the general offices of the Institute of Medicine in downtown Chicago. Organized as a separate corporation, it operates under the jurisdiction of the Institute of Medicine's Committee on Chronic Illness, which acts as the board of directors. This committee includes eight physicians, an administrative nurse, an executive of the welfare council, two lawyers, and four other lay persons.

The agency began operation with a staff of five: a director, a consultant on standards who was a home economist familiar with the development of quality-quantity-cost standards, a nurse and a medical social worker designated as consultants on resources, and an office secretary. With the termination of the special fact-finding phase of the agency's work, the position of consultant on standards was discontinued. An additional typist has since been added, leaving a present active staff of five.

The director of the central service is a registered nurse, with a bachelor's degree. Her duties, in addition to administrative supervision of staff, include reporting to the board on all agency operations and activities and implementing all decisions of this group, formulating new policies and programs, employment of personnel, expenditures of funds, and representing the service to the community.

The two consultants on resources are responsible for the collection and maintenance of information on the available nursing homes, institutions, agencies, and other facilities in the community and for day-to-day counseling with patients and other persons seeking suitable facilities for care. Information is collected and kept up to date through visits, telephone calls, summarizing of reports from agencies, institutions, and patients, and other methods. Much of the work toward improving quality of care is carried on during visits to the homes and institutions, through the provision of consultant service to operators of the facilities, and through the distribution of printed material.

The secretary and a typist handle the major part of clerical-administrative detail inherent in the agency's operation. Their duties include maintaining administrative files of the agency, preparing financial and statistical reports and records, handling staff schedules and payrolls, purchasing of supplies as authorized by the director, and performing stenographic work for the professional staff.

Request for service forms are kept for each patient or other person contacting the central service, giving diagnosis, degree of disability, services requested and needed, action taken, and other pertinent information. The service also maintains detailed individual records on agencies, homes and institutions, sources of financial assistance, and all other resources for long-term care or service in the community, and it has abbreviated this information in a desk card file for quick reference. Finally, the service maintains over-all statistical information on the relationship of needs and resources for care in Chicago. This includes full information about resources for care of patients in their homes and a yearly register of all nursing and old-age homes, hospitals, rehabilitation centers, and other institutional facilities serving long-term patients, giving bed capacity and type of ownership or auspices.

Services to Patients

In line with the central service's policy to act purely as an information and counseling center, rather than as a case-work agency, persons requesting service are accepted without any prior investigative procedures. For this same reason, and because of the expense involved, the service does not attempt any organized follow-up of patients to see whether a satisfactory solution or placement has been completed.

The service has not attempted any community-wide publicity campaign directed toward patients or other agencies. The annual reports of the central service are reprinted in the Proceedings of the Institute of Medicine, and there has been an occasional article or editorial in this publication. Notices of the availability of the service are published from time to time in the Bulletin of the Chicago Medical Society, and descriptive listings are carried in the Welfare Council's Social Service Directory and the classified telephone directory.

There have been a number of informational mailings about the service to physicians in Chicago and Cook County, and a letter and leaflet recently were sent to all physicians in the area, all clergymen, and a selected list of lawyers, trust officiers, and personnel directors in various business and industrial establishments. Finally, there have been sporadic newspaper articles and radio announcements concerning the availability of the service. Current thinking is that more publicity specifically directed toward the service's informational and counseling functions would be helpful.

During the calendar year 1958, a total of 2,892 patients or other persons sought information or counseling at the service center. Of these requests for service, 433 were recall cases, or patients who had previously contacted the center and 314 were requests for service not related to an individual patient. Table 1 shows the number of requests

during 1956, 1957, and 1958, divided by new and recall cases, and other requests not concerned with a specific patient.

A special tally of a randomly selected 100 patients served during December, 1957, shows that 83% of these were over 60 years of age. Three-fifths, or

TABLE 1.—*Persons Served in 1956, 1957, and 1958*

Year	Patients, No.		
	New*	Recall†	Other No.‡
1956	1,569	226	227
1957	1,721	334	225
1958	2,145	433	314

* Patients known to center for first time.
† Patients who have received previous service from center.
‡ Requests for service not related to specific patient.

60% of this group, were women, a proportion which has held relatively constant over the years of operation. Of the cases on which the data were available, 27% of the patients were married and 73% were single, widowed, separated, or divorced; 26% were in hospitals at the time of contact, and an additional 14% were in nursing homes, boarding homes, and other institutions; 14% were living at home with husband or wife, 27% with other relatives or friends, and 19% alone. The proportions of ambulant, semiambulant and bedridden patients referred to the service have been relatively constant since its inception, as have been the number of patients able and unable to pay full costs of care.

Table 2 gives a breakdown of these 100 newly referred cases by age, degree of disability, financial status, source of referral to the service, and other characteristics.

Needs of Patients

During September and October, 1958, nearly 65% of patients contacting the central service for the first time requested nursing home or other institutional care. The next most frequent requests were for some type of housekeeper-attendant service and for general counseling and help in planning a patient's care. Other requests were for information on some specific facility, home nursing care, or rehabilitation services. Table 3 shows the nature of requests for service among 638 calls received by the central service during September and October, divided by new and recall cases. Also included are calls received from nursing home operators on management problems, from persons planning to establish such facilities, and from individuals and organizations seeking general information on needs and resources.

Some 60 to 65% of all patients requesting service are given help in finding homes and institutions providing long-term care. Another 10 to 12% of patients are given information or counseling on home-care services or resources for financial assistance. Five to eight per cent of patients are referred to social case work agencies. Other referrals are to rehabilitation facilities and similar community services. For a small number, further medical or psychiatric evaluation is recommended before attempting a plan for care.

Problems and Developments

The important unmet needs and problems of Chicago's chronically ill, as evidenced by requests to the central service and by its extensive fact-finding work in the community, seem to revolve around a need for substantial improvements in financing of services; a shortage of good inpatient facilities for long-term care; a need for broadening the range of services offered, especially rehabilitation services within the various long-term institutions; some deficiency in the services available to help patients and their families at home; and a need for closer coordination of the activities of the many different organizations now becoming involved in the planning and development of community services in the field of chronic illness.

At present, in Chicago, there are about 16,000 beds for long-term care—in special hospitals for treatment and rehabilitation of the chronically ill; in voluntary, public, and private nursing-care facilities; and in infirmary sections of homes for the aged. Although this represents an encouraging growth from the some 10,000 beds available at the time of the central service's inception, and is not far short of the total number needed, at least 6,000 of these presently available beds are of such poor quality and offer so little possibility of substantial improvement that they should be replaced by new facilities. Most of these 6,000 substandard beds are

TABLE 2.—*Characteristics of One Hundred Patients Newly Referred to Center, December, 1957*

	Patients, No.
Sex	
Male	40
Female	59
Not recorded	1
Age	
<20	2
21-40	2
41-60	10
>60	83
Not recorded	3
Marital status	
Married	23
Single	15
Widowed, divorced, or separated	46
Not recorded	16
Living arrangements	
Alone	17
With spouse	13
With relatives or friends	25
Boarding or nursing home	12
Hospital	24
Other institutions	1
Not recorded	8
Degree of disability	
Ambulatory (includes senile)	45
Semiambulatory	26
Bedfast	28
Not recorded	1
Method of contacting center	
Phone	93
Letter	3
In person	4
Main source of income or support of referred persons*	
Spouse	6
Other relatives and/or friends	24
Old Age Assistance	9
Old Age Assistance, relatives, Old Age & Survivors Insurance, etc.	5
Other public welfare	2
Pensions	16
OASI, savings, relatives	8
Business, employment, rentals	1
Savings only	2
Capital assets, convertible property	3
Disability and employment insurance	...
No income	1
Not recorded (unknown)	5
Private funds (exact source not specified)	18

* Figures are weighted toward self-supporting persons, as arrangements for care of financially dependent usually are made by welfare agencies.

in small proprietary nursing homes in the city, and the central service feels that this is a reflection of two primary factors. One of these is the fact that many of the operators of these facilities have not had the experience or training necessary to provide good care economically and efficiently. Until recently there have been no institutes, training centers, or other educational resources from which these operators could obtain guidance in organizing and operating a nursing home, or even any books or journals devoted to this subject. There has been a definite need, first, for a specific definition of what good care consists of, and what is required to provide it in terms of organization and ownership of nursing home facilities, relationships between these facilities and other inpatient care institutions, physical plant and equipment, numbers and training of personnel required, and costs; and, second, for educational channels through which this information can be made available to the owners and operators of the facilities.

A major part of the central service's work has been directed toward these needs. A 400-page book giving practical guidance for persons planning to establish new homes and institutions has been published by the service, and a companion volume on organization, management, and budgeting procedures is forthcoming. Hospital organizations and journals are publishing material of this type with increasing frequency. A number of short training courses covering patient care, personnel, management, budget, and other such areas have been set up for nursing home owners and operators, and efforts along this line are increasing. The second important factor in the inadequacy of many proprietary nursing homes has been the lack of sufficient funds to provide good care, particularly for public assistance recipients.

The central service continues to urge and work for more realistic standards of payment for public assistance recipients, through its contact with other agencies and individuals in the community, talks and programs before interested organizations, and cooperating with the Health Division of the Welfare Council in efforts to improve the payment standards now in use by the Illinois Public Aid Commission.

Services to the Community

From its inception in 1944 up until 1955, a major part of the central service's work was taken up with various special studies into the nature, prevalence, and problems of chronic illness in the Chicago area. In addition to the broad, day-to-day collection of information on the number, types, and needs of chronically ill, and the community services required to meet these needs, the service has completed the following specialized studies: (1) terminal care for cancer patients—a study of the facilities available and needed in Chicago for care of this group, specially financed by the American Cancer Society; (2) a specially financed study of the services available and needed for home care; (3) the need for institutional facilities for the long-term care of children; (4) the need for special institutional facilities for young adults; (5) an analysis of personnel and services required in different types of homes and institutions for long-term care; and (6) costs of care in long-term institutional facilities, compared with the costs of home services for the chronically ill.

By the end of 1954, the central service had identified and clarified the major problems and unmet needs of the chronically ill in Chicago and had assembled information on the services needed and extent of the need, types and numbers of agencies and institutions required, the pros and cons of various forms of organization of services, probable costs, and the possibilities for financing. The central service has developed and is planning to publish a model plan for a coordinated community-wide program in Chicago directed toward all aspects of the chronic illness problem—early diagnosis and prevention; care and rehabilitation of the long-term patient at home, in hospitals, nursing and old-age homes, and other institutions; coordination of community facilities and services; fund-raising and financing of care; maintenance of statistical information on needs as related to facilities available; and the basic community and professional services needed in research, professional, and public education, and licensing and standard setting for institutions and personnel.

Other material published or about to be published by the central service includes a 25-page pamphlet summarizing methods for surveying community

TABLE 3.—*Nature of Requests for Service Among 638 Calls Received During September and October, 1958*

Type of Request	Percentage of Total Cases		
	New Cases	Recalls	Total
Nursing home, boarding home, institution	64.2	60.3	63.7
Nursing home and financial assistance	2.7	1.4	2.5
Housekeeper, attendant, etc.	7.6	1.3	6.9
Nursing care in patient's home	1.8	...	1.6
Information re facilities and resources			
Sheltered or home employment	0.2	1.4	0.3
Financial assistance	1.6	1.3	1.6
Rehabilitation services	1.6	...	1.4
Wheel chairs, hospital beds, etc.	0.3	...	0.3
Medical and dental care, free or cheaper medicines	0.4	...	0.3
Transportation to clinics	0.2	...	0.2
Recreation and companionship plus medical and dental care	0.2	...	0.2
Day care	...	...	...
Restaurants serving special diets	...	...	...
Miscellaneous procedures, legal advice, camp, etc.	0.3	...	0.3
Information regarding a specific facility	4.1	5.5	4.2
Help in formulating specific plan for care of patient, information about various types of facilities	6.2	5.5	6.1
Information on costs of care	0.3	...	0.3
Consultation to nursing home managers on management problems	1.6	...	1.4
Consultation to persons planning establishment of new facilities	2.3	...	2.1
Consultation to persons and organizations seeking information about care of chronically ill (including statistical data, information on costs of care, and standards)	4.4	...	3.9
Additional information only	...	23.3	2.7
Total	100	100	100

needs and resources for long-term care; a 55-page booklet on the role of the nurse in caring for the chronically ill; a monograph on community services for rehabilitation; a monograph on licensing and standard-setting for long-term care institutions; a casework manual for welfare agencies to assist them in arranging care for the chronically ill patient; and a monograph on home-care services.

Finally, the professional staff of the service continues on a day-to-day basis to counsel with the operators of institutions providing long-term care, particularly privately owned nursing homes, in efforts to develop and maintain good standards of care, and to maintain and make available to the community centralized information about the needs and resources for care of the chronically ill in the Chicago area.

CENTRAL AGENCY FOR THE CHRONICALLY ILL OF MILWAUKEE

The Central Agency for Chronically Ill, of Milwaukee, was established in February, 1948, as the result of a two-year study into the problems and unmet needs of chronically ill persons in Milwaukee County. This study, which was financed by the Women's Club of Wisconsin and conducted by a special study committee of physicians and other citizens appointed by the Community Welfare Council of Milwaukee County, showed a need for some type of central clearing house to collect information on the facilities providing long-term care and the additional facilities and services needed in the county. The study committee was then charged with developing, in cooperation with other agencies, a central information-gathering and educational service for the chronically ill.

The central agency was supported through its first years by a grant of $10,000 from a service club and presently by the Community Chest, of which it is a participating agency. Its objectives are (1) to gather and maintain current information on nursing homes, homes for the aged, and other facilities providing service for the long-term patient and to assist with placements in these facilities; (2) to stimulate through community education the setting aside of additional hospital beds for long-term illness, the expansion of good nursing home facilities, the extension of bedside nursing care in private homes, and the development of additional facilities for recreation and rehabilitation; and (3) to stimulate further study of degenerative diseases from all aspects.

Organization and Operation

The central agency occupies a small office in the downtown Milwaukee area. The original staff consisted of the executive director and an office secretary. A professional staff worker was added as operations progressed. The central agency functions under the supervision of a 21-man board of directors, representing the fields of medicine, industry, finance, law, the clergy, public relations, and service groups. This board, which meets once monthly, is responsible for over-all policies of the agency and for approving budget expenditures and any changes or additions in the agency's program. The agency is organized as a corporation, with an unlimited number of members who are elected for five-year terms. These members represent various fields and professions in the community, participate in special program meetings several times a year, and serve as a reservoir from which to draw new members for the board of directors.

The executive director of the agency is a registered nurse, with a masters degree in public health. Her duties, in addition to over-all administrative supervision of the agency and preparation of the budget, include formulating new programs and policies for the agency and submitting them to the board of directors and the Community Welfare Council, interpretation of agency policies and programs to the community, developing educational programs and institutes directed toward the general public and various professional groups, securing data and preparing reports on the individual and community problems of long-term illness, and continuous liaison with other community social and health agencies in order to foster a coordinated approach to problems of the chronically ill.

The professional staff worker is a registered nurse with a degree in public health nursing. Under supervision of the executive director, she is responsible for counseling and referral of patients seeking nursing homes and other facilities for care, for visiting and evaluating all nursing, old-age, and foster homes within a 50-mile radius of Milwaukee, for keeping a running file on these facilities, and for consulting with persons planning new nursing homes and other such facilities in regard to standards of care. Her duties also include meeting regularly with state and local organizations of nursing home operators and assisting these operators with problems related to management efficiency, nursing care, and costs.

The office secretary handles most clerical-administrative detail in the agency's operation, including typing, maintaining files and records, and serving as receptionist and telephone operator. Monthly narrative, statistical, and financial reports on the agency's operation, in addition to an annual report, are prepared jointly by the director and the staff worker and distributed to the board and all corporation members. Other records and files maintained in the office include request-for-service forms for all patients or other persons seeking information—these include diagnoses and the name of the

physician in charge for all patients—a complete nursing home evaluation report on all facilities visited by the staff worker and a summary of these evaluation reports in a desk card file. The agency also maintains a reference library of books and other educational material.

Services to Patients

About one-fourth of the time of the professional staff is taken up with counseling and referral of patients to nursing homes or other institutions and services for the chronically ill. The central agency has not attempted any intensive publicity toward this facet of its operation. Articles noting the availability of the counseling service have been published from time to time in the local newspapers, and the agency has published brochures or pamphlets directed toward persons seeking information on the services available in Milwaukee.

TABLE 1.—*Characteristics of Patients Newly Referred to Center in 1957*

	Patients, No.
Sex	
Male	199
Female	314
Age	
<80	2
21-40	17
41-60	47
>60	447
Marital status	
Married	72
Single	91
Widowed	305
Divorced or separated	2
Not recorded	43
Living arrangements	
Alone	126
With spouse	64
With relatives or friends	115
Boarding or nursing home	20
Hospital	126
Other institution	48
Not recorded	14
Degree of disability	
Ambulatory	146
Semiambulatory	241
Bedfast	126
Method of contacting center*	
Phone	437
Letter	27
In person	99
Main source of income or support of persons referred	
Spouse	24
OAA plus relatives, OASI, etc.	62
Pensions (retirement, veterans, etc.)	47
OASI plus savings, relatives, etc.	39
Income from business, employment, or rentals	338
Savings only	
Capital assets, convertible property	
Not recorded (source unknown)	3

* Includes more than one type of contact by some patients.

Patients seeking information or placement counseling are accepted for service without any prior investigative or casework procedures. The agency has at times had sample clearances with the Social Service Exchange in Milwaukee but decided against making it a routine practice. The agency does not attempt any organized follow-up of patients to see whether the referral or placement made in individual cases has been completely satisfactory.

The number of patients and other persons seeking help at the agency has increased slowly but steadily since its inception in 1948. In the fiscal year 1954-1955, 619 new patients or other persons contacted the agency for service; in 1955-1956, 688, and in 1956-1957, 693 new patients were served by the agency. At present patients are referred to the agency by their families, themselves, the Visiting Nurse Association, hospitals in Milwaukee, physicians, lawyers and courts, and friends, in about that order of frequency.

Of the 513 individual patients referred to the agency during the calendar year 1957, over 85% were 60 years of age or older. This age percentage has held relatively constant over the years of operation, with an average patient age near 75. Over three-fifths of patients referred to the center were women, a proportion which has also held constant. About 77% of the patients were widowed or single, 25% lived alone, and 22% lived with relatives. An increasing percentage of bedfast or incapacitated patients have sought help at the agency in recent years. The percentage of senile or mentally disoriented patients referred to the agency has also risen. Table 1 shows the characteristics of individual patients referred to the agency during the calendar year 1957 by age, degree of disability, living arrangements, financial status, and other factors.

Needs of Patients

In the period from October, 1957, through September, 1958, requests for 24-hour nursing, boarding, or other institutional care accounted for a little over 36% of all needs for service among newly referred patients or other persons. The next most frequent requests were for counseling or educational material. Other frequent requests among new contacts were for information on establishing a new facility for care and for information on sheltered or home employment and custodial day care. Table 2 shows the nature of requests for service received during this period, divided according to new and recall patients. Not included in this tabulation are some 259 calls received from nursing home operators during this period, reporting vacancies or the filling of vacancies in their facilities.

The community facilities or services to which patients are most frequently referred have been nursing and old-age homes, the Welfare Department, Visiting Nurse Association, the Family Service Agency, and the local Old-Age and Survivors Insurance (OASI) Bureau.

Problems and Developments

As a result of its referral and fact-finding work with patients and other individuals and agencies in the community, the central agency has been able to pinpoint some of the more pressing problems in meeting the needs of Milwaukee County's chronically ill. There is an urgent need at present for some type of visiting homemaker or housekeeper service which could be made available to the considerable number of chronically ill or infirm patients living at home. Such a service has been approved by the Visiting Nurse Association, but its inception has been delayed by a difficulty in recruiting housekeepers. The central agency is also planning to inaugurate, on a demonstration basis, an organized home-care program similar to those operating in other communities. This project is presently awaiting the approval of the Milwaukee Medical Society.

Another major problem is the lack of suitable facilities for care of the "in-between" type of senile patient, who is too much of a supervisory problem for the average nursing home operator but does not need or belong in a mental institution. Progress on this problem has been nil to date. There is also a lack of suitable nursing care facilities for persons in the middle and higher income group who desire and are able to pay for a private room and bath. The central agency, in its consultation work with nursing home operators, has stimulated those persons planning new or improved facilities to include more such private and semiprivate accommodations in their planning.

Finally, the agency feels that there is a definite need for additional organized inpatient rehabilitation services. Milwaukee has adequate rehabilitation services at the outpatient level, but more inpatient facilities than those presently provided by the general hospitals of the city are needed.

Services to the Community

More than 40% of the working time of the director and staff worker is taken up with activities of a community-wide nature—classes, talks and other educational projects, visits to nursing homes and counseling with their operators, and assistance to nursing home organizations, both state and regional. The central agency has sponsored, organized or participated in a number of annual workshops for nursing home operators. These workshops have utilized the educational resources of a number of state and local agencies and organizations and have covered such areas as nursing service, nutrition, rehabilitation, administration, budgetary and management problems, enlistment and training of nursing home personnel, and broad trends in the nursing home field. The first such workshop was given by the agency in Milwaukee in 1951, with the help of the newly formed Milwaukee County Nursing Home Association. Two similar programs were given in the years following, and in 1954 a statewide workshop was held in Milwaukee in cooperation with the Marquette College of Nursing and the State Nursing Home Association. Another statewide program was held in 1955, conducted jointly by the central agency, the University of Wisconsin Extension Department, the State Health Department, and the State Nursing Home Association; similar workshops have been given up to the present.

The central agency has compiled and published a small fact booklet on the patients in Milwaukee's proprietary nursing homes. The booklet gives statistical information on age, sex, diagnoses, types of care required, referral sources, patient income, and costs of care. These data were obtained with a special questionnaire used by the staff worker in the course of her routine nursing home visits.

Other informational and educational material published and distributed by the agency includes a brochure on the important problems of chronic illness written for the general public, a 12-page booklet giving some of the general points to be considered by patients and their families in selecting a nursing home, and a similar booklet highlighting some of the essential problems in the operation of a nursing home, directed toward administrators of these facilities.

A recent project has been the mailing of a quarterly "Food Notes" bulletin to nursing home operators and cooks. This 2-to-4-page bulletin, which is prepared with the help of the Milwaukee Health Department nutritionist, notes some of the plentiful and easily obtained foods in a particular season, gives suggestions for their use in menus, and contains recipes in serving quantities for from 10 to 50 persons. Suggestions are also given on attractive and efficient serving methods, special dishes, and the like.

TABLE 2.—*Nature of Requests from Oct. 1, 1957, to Sept. 30, 1958*

	New Cases	Recalls*	Total
Nursing Home, boarding home, institution	517	154	671
Housekeeper, attendant, etc.	34		34
Information re facilities and resources			
Sheltered or home employment	47		47
Financial assistance	15		15
Wheel chairs, hospital beds, etc.	9		9
Rehabilitation services	5		5
Free or cheaper medicine	2		2
Housing	6		6
Transportation to clinics	2		2
Day care (custodial)	45		45
Restaurant serving special diets	3		3
Establishing new facility	79		79
Consultation, educational material	246		246
Counseling	277		277
Additional information only	141		141
Total	1,428	154	1,582

* Persons previously receiving service from agency

The director of the central agency is co-author of a book on the care and rehabilitation of the chronically ill; she continues to write articles and develop exhibits, literature for distribution, and other educational material on the general and specific problems of the chronically ill and their care.

The central agency is currently investigating the possibilities for future study and action in such areas as encouraging the development of new skilled nursing care facilities by church and other nonprofit groups, who have not been too active in this field in the past, possible contributions by the general hospital in improving long-term care, improved methods of caring for the homebound chronically ill, and a study of the incidence of chronic disease in certain special groups, such as the Negro population and industry. The agency continues to work toward fostering an enlightened public attitude toward the problems of the aged and chronically ill and to stimulate the coordination of community facilities and services in meeting these problems.

MEDICAL NEWS

ARIZONA

Annual Meeting in Chandler.—Preliminary plans for the 68th annual meeting of the Arizona Medical Association in Chandler, April 30-May 2, were announced by Dr. Dermont W. Melick, of Phoenix, chairman of the scientific assembly committee. Papers will be presented by Drs. Haddon M. Carryer, Mayo Clinic; John W. Cline, Stanford University; Harold D. Jenkins and Marvin E. Johnson, University of Colorado; Henry H. Kessler, Kessler Institute for Rehabilitation; Johannes M. Nielsen, University of California at Los Angeles School of Medicine; and Thomas L. Royce, Baylor University. As a special feature, a medical education workshop will be held May 1. Presentations on medical education will be given by Dr. John Z. Bowers, University of Wisconsin; Fred Dow Fagg Jr., Ph.D., president, Western Interstate Commission for Higher Education; Mr. Reuben Gustavson, president, Resources for the Future; Walter L. Hard, Ph.D., University of South Dakota; and Drs. Marvin E. Johnson, University of Colorado; Vernon W. Lippard, Yale University; Roscoe L. Pullen, University of Missouri; Thomas L. Royce, Baylor University; and Thomas B. Turner, Johns Hopkins University. Moderator will be Dr. John W. Cline, Stanford University. The meeting will be held in the San Marcos Hotel. Officers of the association are Dr. Wilkins R. Manning, Tucson, president; Dr. Dermont W. Melick, Phoenix, president-elect; Dr. Lindsay E. Beaton, Tucson, vice-president; Dr. Leslie B. Smith, Phoenix, secretary; and Dr. Clarence E. Yount Jr., Prescott, treasurer.

ARKANSAS

Annual Session Planned at Fort Smith.—The 83rd annual session of the Arkansas Medical Society will be held April 12-15 at the Goldman Hotel, Fort Smith. The president's address will be given the morning of April 13 by Dr. Louis K. Hundley, Pine Bluff. "Third Party Payment for Medical Care" will be presented by Dr. Frank C. Coleman, Des Moines, president, College of American Pathologists, that afternoon. Out-of-state speakers include the following:

Drs. Harold O. Perry, Rochester, Minn.; Lt. Col. George R. Steinkamp, M.C., U. S. A. F., Randolph AFB, Texas; I. Frank Tullis, Memphis, Tenn.; J. E. Markee, Durham, N. C.; M. T. Jenkins, Dallas, Texas; Conrad G. Collins and Edgar Burns, New Orleans; Hugh F. Hare and Howard House, Los Angeles; Harris D. Riley, Oklahoma City, Okla.; William Dameshek and Kenneth W. Warren, Boston.

Specialty section meetings are planned for April 14, with the annual banquet to be held that evening. Dr. F. J. L. Blasingame, Executive Vice-President, American Medical Association, will address the House of Delegates the afternoon of April 12. Films and exhibits are arranged. Entertainment includes a golf tournament. For information write Mr. Paul C. Schaefer, Kelley Bldg., Fort Smith, Ark., Executive Secretary.

COLORADO

Plan Expansion of Tuberculosis Research Facilities.—The Colorado Foundation for Research in Tuberculosis, housed in the Webb building on the University of Colorado Medical Center campus, Denver, will add a third floor to the structure to expand its facilities for research in biochemistry and the genetics of bacteria. Dr. Roger S. Mitchell, director of the foundation, said the organization has the necessary funds to move forward with construction as soon as the Board of Regents approves the details. He added that Dr. Oscar Reiss, of the Johns Hopkins University School of Medicine, Baltimore, will join the staff in June to head this new activity. The Colorado Foundation for Research was established in Colorado Springs in 1922 by the late Dr. Gerald E. Webb, and was moved to the Medical Center campus in 1954. Dr. James J. Waring, professor of medicine emeritus, at the School of Medicine, is the foundation president.

DISTRICT OF COLUMBIA

Dedicate Hospital Research Center.—On March 22 Children's Hospital of the District of Columbia dedicated its new Children's Hospital Variety Club Research Center. Dedication speaker was Dr. Leroy E. Burney, Surgeon General, U. S. Public Health Service. The research center, located next to the hospital, at 12th and W Streets, N., was built at a cost of about $800,000, financed in part by grants totaling $484,000 and by a contribution of $200,000 from the Variety Club of Washington. Additional funds are being raised in a campaign for $460,000 launched last November. The Children's Hospital Variety Club Research Center, which commemorates the Variety Club's Chief Barker, Fred S. Kogod, is a modern building with three floors and a basement. The front is of heavy, opaque glass

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

and aluminum, and the sides are of brick to complement existing hospital buildings. In the air-conditioned building all necessary services (water, electricity, gas, compressed air) will be available in each research unit. Movable partitions will allow rearrangement of research areas without extensive repairs and remodeling. In addition to the laboratories of the seven research sections there is a radioisotope laboratory and a large sterilizing room with equipment for washing and sterilizing glassware. The Research Foundation of Children's Hospital was incorporated in 1947 to further pediatric research at Children's Hospital. Its president is Dr. Edgar W. Davis, and the director of the foundation is Dr. Robert H. Parrott, physician-in-chief of Children's Hospital.

HAWAII

Annual Convention in Hilo.—The Hawaii Medical Association will hold its 103rd annual meeting in Hilo April 23-26 at the American Legion Hall. Panel discussions on "Coping with the Teenager" and "Hernia Hydrocele and Undescended Testicle" will be moderated by Drs. J. Roswell Gallagher, Boston, and Tague C. Chisholm, Minneapolis, respectively. The following papers are scheduled:

Rehabilitation of the Hemiplegic, Dr. R. Frederick Shepard.
Cerebral Hematoma, Dr. John J. Lowrey.
Portal Hypertension, Experiences in the Management of Hemorrhage from Esophageal Varices, Dr. Gilbert C. Freeman.
Improving Medical Certifications of Death, Dr. Halbert L. Dunn.
Pitfalls in Surgery of the Hand, Dr. Leabert R. Fernandez.
Surgical Approach to Fascial Space Infection in the Hand, Dr. Raymond G. Chang.
Study of Lipoproteins in the Nisei, Dr. Kyuro Okazaki.
Report on Coronary Atherosclerosis in our Different Ethnic Groups from a Successive Series of 2,000 Autopsies, Dr. Nils P. Larsen and Dr. Walter M. Bortz.

The presidential address will be given by Dr. William N. Bergin. Exhibits are planned, and the annual golf tournament will be held April 26. Woman's auxiliary activities include a golf tournament April 25. Registration fee is $10.

ILLINOIS

Chicago

Visiting Pathologist.—Dr. R. Winston Evans, pathologist of Liverpool, England, has started teaching as temporary visiting professor of pathology at the University of Chicago. He is lecturer in the department of clinical pathology at the University of Liverpool and a consultant pathologist at the David Lewis Northern Hospital and the St. Paul's Hospital in Liverpool.

Dr. Jensen Receives Pasteur Award.—Lloyd B. Jensen, Ph.D., was chosen to receive this year's Pasteur Award, the Society of Illinois Bacteriologists announced. Formal presentation of the sterling silver medal and cash award will be made April 11 at a dinner meeting of the society in the Morrison Hotel. The Pasteur Award is given for "notable contributions to the science of bacteriology." The award is given to Dr. Jensen "for his outstanding contributions to food microbiology." For 27 years prior to retirement in April, 1958, he was chief bacteriologist at Swift and Company. He also lectured for 16 years at the U. S. Army Meat and Dairy Hygiene School on Pershing Road. In 1954 he was appointed consultant to the Walter Reed Army Institute of Research by the Surgeon General. Dr. Jensen was one of the founders and early editors of the journal, *Food Research*.

Appoint Dr. Kronfeld Department Head.—Appointment of Dr. Peter C. Kronfeld, of Wilmette, as professor and head of the department of ophthalmology, University of Illinois College of Medicine, was approved March 12 by the board of trustees. Dr. Kronfeld also was named ophthalmologist-in-chief of the University of Illinois Hospital and the Illinois Eye and Ear Infirmary. He has been professor of ophthalmology at the U. of I. College of Medicine and attending ophthalmologist at the infirmary since 1947. He joined the faculty of the university's professional colleges in 1943. Dr. Kronfeld succeeds Dr. William F. Hughes, also of Wilmette, who resigned the positions last September, but has continued on the College of Medicine staff as clinical professor of ophthalmology. Dr. Howard L. Wilder, assistant professor of ophthalmology, has been acting head of the department. Dr. Kronfeld received his M.D. from the University of Vienna and joined the staff of the University of Chicago in 1927 and remained there until 1933.

KANSAS

Annual Lecture Given.—The annual Clendening Lecture at the University of Kansas School of Medicine, Kansas City, was delivered by Dr. Edward H. Hashinger, professor emeritus of medicine and gerontology, on March 12. "Arthur E. Hertzler—the Kansas Horse and Buggy Doctor" was the subject of his tribute to the Kansas physician who was on the faculty of the school for over 30 years prior to his death in 1946. The Clendening series was established in 1949 by the widow of the late Dr. Logan Clendening, a pioneer in medical education at the Kansas School. Dr. Hashinger had residency training in the Halstead, Kansas, Hospital founded by Dr. Hertzler, who received international recognition for his best-seller, "The Horse and Buggy Doctor."

MASSACHUSETTS

Dr. Fulton Named First Warren Professor.—Prof. George P. Fulton, Ph.D., of Lexington, chairman, department of biology, Boston University's College

of Liberal Arts, was named to the first Shields Warren Professorship at Boston University, according to an announcement by President Harold C. Case. The chair was established a year ago on the occasion of the 60th birthday of Dr. Shields Warren, of West Newton, pathologist and chairman of the executive committee of the Boston University board of trustees. At that time, some 700 Greater Bostonians donated funds to establish the professorship at Boston University, in honor of Dr. Warren, whose grandfather was the university's first president. Dr. Fulton was a pioneer in the use of the hamster cheek pouch method of studying the small blood vessels. Last year, Dr. Fulton was a visiting professor of physiology at the Stanford University School of Medicine in San Francisco for seven months. He is associate editor of *Angiology* and a fellow and vice-president of the American College of Angiology.

MICHIGAN

Annual Cancer Day in Flint.—The Genesee County Medical Society will present its 14th annual Cancer Day, April 22, at the Merliss Brown Auditorium, Hurley Hospital, Flint. Dr. Jackson E. Livesay, president of the society, will open the meeting with an address. Presiding officers at the forenoon and afternoon sessions will be Drs. G. B. Saltonstall, president, Michigan State Medical Society, Charlevoix, and James W. Logie, president, Kent County Medical Society, Grand Rapids. Topics and speakers are as follows:

The Current Status of Interstitial Irradiation, Dr. Ulrich Henschke, New York City.

Head and Neck Cancer as Seen in the Oral Cavity, Dr. Danely P. Slaughter, Chicago.

The Current Status of Cancer Research, Dr. Freddy Homburger, Cambridge, Mass.

The Problem of Soft Tissue Tumors as Seen by the Surgical Pathologist, Dr. Raffaele Lattes, New York City.

Extended Operations for Cancer of the Stomach and Colon and the Second Look, Dr. Owen H. Wangensteen, Minneapolis, Minn.

The Problem of Pigmented Mole and Malignant Melanoma, Dr. George T. Pack, New York City.

MISSISSIPPI

Annual Meeting of State Psychiatrists.—The newly formed Mississippi Psychiatric Society, a district branch of the American Psychiatric Association, held its first annual meeting on March 7 at the University of Mississippi Medical Center, Jackson. Dr. J. G. N. Cushing of Baltimore, southern area representative on the policy committee of the Assembly of District Branches, addressed the group on historical aspects of the American Psychiatric Association and the formation of district branches. Dr. Hamilton F. Ford, of the University of Texas Medical Branch, Galveston, gave the academic lecture on "Phrenotropic Drugs—Applicability Based on Chemical Grouping." Dr. Floy Jack Moore, chairman, department of psychiatry, University of Mississippi Medical Center, was elected president to succeed Dr. Frank A. Donaldson, of Jackson. Others elected as the first complete slate of officers were: president-elect, Dr. Lawrence G. Behan, Gulfport; secretary-treasurer, Dr. L. C. Hanes, Jackson; council member, Dr. John J. Head, Whitfield; delegate to assembly of district branches, Dr. William L. Jaquith, Whitfield; and alternate delegate, Dr. Beverley E. Smith, Jackson.

MISSOURI

Hospital Lecture.—The Jewish Hospital of Saint Louis announced that the 12th Jack H. Tritt Memorial Lecture was given April 2 by Dr. Edwin P. Hiatt, chief, Aero Medical Laboratory, Wright Air Development Center, Dayton, Ohio, on "Medical Problems of Manned Space Flight."

NEBRASKA

Student Aid Fund Established.—A fund to aid needy students in medicine has been established by a group of physicians at the University of Nebraska College of Medicine, Omaha. The charter members are all on the staff of the university. A nonprofit corporation without capital stock, the Nebraska Medical Education Fund, Inc., is "for educational and charitable purposes." Aid will be given regardless of race or creed. The main purpose of the organization is "to help needy and worthy students in medical and health professions to obtain higher education." The corporation has the authority to accept contributions and invest them, borrow money, and pay and obligate itself for any expenses involved. Loans to one student for one academic year may not exceed $1,500. Applications can be obtained from the Student Assistance Committee through the office of the assistant dean. To be a member with full voting rights, one must be licensed to practice medicine in Nebraska. However, honorary members may be named. Officers of the corporation are Dr. Clinton C. Millett, president; Dr. Willson B. Moody, vice-president; and Dr. John R. Schenken, treasurer.

NEW YORK

State Society Convenes in Buffalo.—The Medical Society of the State of New York will hold its 153rd annual convention May 9-15 at the Hotel Statler-Hilton, Buffalo. The annual dinner, at which Dr. Gunnar Gundersen, President, American Medical Association, will be the principal speaker, will take place the evening of May 11. The program will consist of general sessions, sections, exhibits, and films. Symposiums and panel discussions on Surgery in Cardiovascular Disease, Prognosis in Surgically Treated Cancer, Hypnosis in Clinical Practice, and the Role of the General Hospital in the Care of Special Medical Problems are planned.

A session on the History of Medicine is set for May 15, 9 a. m., at which time the section on legal medicine will open. The opening session of the regular annual meeting of the House of Delegates will be convened at 10 a. m., May 9, by the speaker, Dr. Joseph A. Lane, of Rochester. At this session Dr. John D. George Sr., of Verona (Oneida County), will receive the State Medical Society award as "Outstanding General Practitioner of New York State for 1958." At the annual dinner, the president's medal will be awarded to Dr. Leo E. Gibson, of Syracuse. He will be succeeded by Dr. Henry I. Fineberg, of Jamaica (Queens County, New York City).

Report on Health Statistics.—A record 362,000 births were reported in New York during 1958; the death rate, 10.4 per 1,000 population, was the third lowest in the history of the state; the tuberculosis death rate, 8.1 per 100,000 was an all-time low; and mortality from cancer was the lowest in eight years. This information is contained in "New York's Health," the 1958 annual report of the New York State Health Department available for distribution. Dr. Herman E. Hilleboe, state health commissioner, explained that the climb in birth rates and the declining death rates have combined since 1950 to increase the population of the state by 1,500,000 persons, giving impetus to the establishment of full-time county health departments. During the year Monroe, Dutchess, and Chemung counties began operation of such units; seven counties with 100,000-plus populations have yet to do so. Advances cited in the report include the work being done at Roswell Park Memorial Institute and the State Rehabilitation Hospital at West Haverstraw; establishment of a 15-station air sampling network by the Air Pollution Control Board; conducting baseline surveys of natural radiation; further development of the state-wide meat inspection program; activities in the field of environmental sanitation, medical services, and local health service; and the research and service activities of the department's Division of Laboratories and Research.

New York City

Dr. DeVoe Named Department Chairman.—The appointment of Dr. Arthur G. DeVoe as professor and chairman of the department of ophthalmology, Columbia University College of Physicians and Surgeons, was announced March 15. At the same time, the appointment of Dr. DeVoe as attending ophthalmologist and director of the ophthalmology service in Presbyterian Hospital was announced. The appointments are effective July 1, when Dr. John H. Dunnington retires from those posts. Dr. DeVoe was a resident in ophthalmology at the Institute of Ophthalmology at Presbyterian Hospital from 1937 to 1940. He served as an associate in ophthalmology in the College of Physicians and Surgeons from 1940 until 1950, when he became professor and chairman of the department of ophthalmology in the New York University Post-Graduate Medical School.

Personal.—Dr. Nadene Coyne has been appointed coordinator of training for physicians in the department of physical medicine and rehabilitation of New York University–Bellevue Medical Center and director of the Respirator Center at Goldwater Memorial Hospital. She was formerly director of the department of physical medicine and rehabilitation, Cleveland General Hospital, Cleveland.—Dr. James A. Brussel, assistant commissioner, New York State Department of Mental Hygiene, will have his novel, "Just Murder, Darling," published by Charles Scribner's Sons; July release is anticipated. Dr. Brussel is also completing "Psychiatry for the Layman" for Barnes and Noble.—Dr. Alexander B. Gutman, director, department of medicine, Columbia University College of Physicians and Surgeons, delivered the annual John Auer lecture sponsored by Phi Beta Pi medical fraternity, Saint Louis University School of Medicine, March 13.

Visit by Foreign Public Health Physicians.—An international group of 26 graduate physicians pursuing advanced studies in public health at Harvard visited the State University of New York Downstate Medical Center, Brooklyn, March 18 and 20 to observe the teaching and research program in environmental medicine. The group was led by Dr. Brian MacMahon, head, department of epidemiology at Harvard. Representing 13 countries in North and South America, Europe, and Asia, the group included 18 physicians who will be returning to faculty positions in preventive medicine in their own countries as well as eight physicians taking the advanced degree program in epidemiology. For some of the group, the visit to the Downstate Medical Center is part of a "peripatetic seminar" program which will include visits to other preventive medicine teaching centers in the United States, the United Kingdom, Puerto Rico, Yugoslavia, and Lebanon.

Dr. Goldwater Honored.—Dr. Leonard J. Goldwater, professor of occupational medicine, Columbia University School of Public Health and Administrative Medicine, received an award from the President's Committee on Employment of the Physically Handicapped and the New York State Governor's Committee on "Employ the Physically Handicapped" March 19 "for contributions in eliminating prejudice and misinformation regarding the rehabilitation of heart patients." The nomination submitted for Dr. Goldwater cited him for his work in organizing the Cardiac Work Classification Unit at Bellevue Hospital in New York City in

1941. This unit was designed to study employment problems of cardiac patients and to study the effects of employment on heart disease and the effects of heart disease on the ability to work. Dr. Goldwater was installed recently as president of the American Academy of Occupational Medicine. He is a member of the World Health Organization expert advisory panel on social and occupational health and is a consultant to the office of vocational rehabilitation, Department of Health, Education, and Welfare.

Scholarship for Advanced Study Abroad.—In the current year the Committee on Medical Education, New York Academy of Medicine, will award one scholarship grant in the amount of $4,500 for the academic year 1960-1961. This scholarship was established to provide aid for advanced study abroad in a clinical subject in preparation for the practice of medicine or surgery in any of their branches. As stipulated by the donor, candidates must be male interns or residents in voluntary, municipal, or Veterans Administration hospitals in New York City. The course of study, the auspices under which it is to be taken, and the place or places where the study is to be pursued must receive the approval of the committee. Applicants are favored who, from their records, show themselves capable of advanced work in clinical medicine. The committee stipulates that the study be pursued abroad, preferably in Great Britain or in continental Europe. Applications for this scholarship must be submitted by Sept. 1. Candidates may secure application forms by writing: Dr. Robert L. Craig, Executive Secretary, Committee on Medical Education, The New York Academy of Medicine, 2 E. 103 St., New York 29.

NORTH CAROLINA

Appropriations for Public Health.—The Raleigh *News and Observer* has reported that per capita state appropriations for public health in some of the Southern states for 1958 were as follows: Georgia, $1.73; Florida, $1.49; Virginia, $1.27; Kentucky, $0.98; Tennessee, $0.89; South Carolina, $0.85; Mississippi, $0.81; and North Carolina, $0.70. While local health departments in North Carolina were established on a basis whereby the state and county share the expenses equally, it is said that the state has gradually lagged in its support of this work until now the counties bear 77% of the cost, the state only 17%, and the remaining 6% comes from other sources.

Scholarships for Medical Study.—Winners of the second eight Reynolds Scholarships for study at Bowman Gray School of Medicine have been announced by Dr. C. C. Carpenter, executive dean. The scholarships, provided by the A. Smith Reynolds Foundation, are adequate to cover the cost of a medical education, including four years of medical school and two years of postgraduate hospital training. Benefits range from $2,400 to $4,800 a year. Reynolds Scholars are chosen by the Committee on Admissions from residents of North Carolina who are admitted to the next entering class at Bowman Gray. Selection is based on character, scholarship, potential as a physician, and financial need. The recipients must have the intention to practice medicine in North Carolina for at least five years after completing their medical education. The first eight Reynolds Scholars will complete the freshman year at Bowman Gray in June. The second eight will enroll in September.

Conference for Medical Record Personnel.—A Conference on Medical Records will be held April 27-29 at the Duke University Medical Center. Planned for hospital medical record personnel and hospital administrators, the conference will be sponsored by Duke in cooperation with the Association of Medical Record Librarians of North Carolina. The second day of the conference will be designed especially for hospital administrators as well as for medical record personnel. Guest speakers who will join Duke Medical Center staff members in presenting the conference program include Margaret J. Heath, president, American Association of Medical Record Librarians, Buffalo, N. Y.; Howard M. Kline, chief, Education and Training Branch, Division of International Health, U. S. Public Health Service, Washington, D. C.; Margaret C. Doran, chief, Medical Record Library Division, Veterans Administration Department of Medicine and Surgery, Washington, D. C.; Donald Smith, administrative assistant, Medical Education for National Defense, Washington, D. C.; Dr. Robert R. Cadmus, director N. C. Memorial Hospital, Chapel Hill; Sample B. Forbus, administrator, Watts Hospital, Durham; and Margaret L. Russell, president, N. C. Association of Medical Record Librarians, Winston–Salem. The conference will be open to North Carolina and to out-of-state medical record personnel and hospital administrators. For information, write Mrs. Je Harned Bufkin, Medical Record Library, Duke University Medical Center, Durham, N. C.

PENNSYLVANIA

Tuberculosis Meeting in Scranton.—The Pennsylvania Tuberculosis and Health Society will hold its annual meeting in collaboration with the Pennsylvania Trudeau Society, Pennsylvania Chapter, American College of Chest Physicians, and the Pennsylvania Conference of Tuberculosis Workers April 15-17 in Scranton. The meeting is acceptable for five hours of category II credit by the American Academy of General Practice. Dr. David A. Cooper will preside at a "Consecutive Case Conference" the morning of April 16. A discussion, "A New Chal-

lenge: Respiratory Diseases," is planned for April 15. Coffee conferences the morning of April 17 will have the following titles and participants:

Tuberculosis, Drs. John S. Packard, Milton, John C. Sanner, Scranton, and Samuel C. Stein, Philadelphia.
Emphysema, Drs. Richard T. Cathcart and Henry P. Close, Philadelphia.
Silicosis, Drs. Ross K. Childerhose, Harrisburg, and Peter A. Theodos, Philadelphia.
Other Acute Respiratory Diseases, Drs. Harold L. Israel and Robert L. Mayock, Philadelphia.

A panel on "Social Implications of a Changing Tuberculous Population" will be conducted the morning of April 16.

Philadelphia

Plan Alumni Publication.—*Medical Affairs*, a new medical alumni and faculty publication has been launched jointly by the School of Medicine and Graduate School of Medicine of the University of Pennsylvania. It will be published four times a year in the spring, summer, fall, and winter. *Medical Affairs* will not be a scientific publication. It will contain editorials by leaders in fields of interest related to medicine, articles by faculty and alumni, news of developments at the schools, news of alumni, book reviews, and activities of the faculty members. More than 14,000 copies will go to Pennsylvania medical alumni in 50 states and around the world. The editorial office of *Medical Affairs* is located at 201 S. 34th St., Philadelphia 4.

Symposium on Structure of Science.—A symposium on "The Structure of Science" will be held April 17-18 accompanying the formal opening of new laboratories and a new museum at the Wistar Institute of Anatomy and Biology. Senator Lister Hill, of Alabama, and Dr. LeRoy Burney, surgeon general, U. S. Public Health Service, will be among the speakers. Mayor Richardson Dilworth will discuss Philadelphia as a center for basic research. The symposium will be held in Irvine Auditorium, University of Pennsylvania, and the institute will be the scene of a reception and a tour of its new laboratories and museum April 18, following the afternoon session. Papers by foreign participants include: "Theories of Tolerance," Dr. Peter B. Medawar, Jodrell professor of zoology, University College, London; "The Structure of Viruses," Dr. Francis H. C. Crick, member of the medical research council's unit for molecular biology at Cavendish Laboratories, Cambridge, England; "Chemical Structure and Biological Function," Dr. H. Gobind Khorana, head of organic chemistry, British Columbia Research Council, University of British Columbia; "The Evolution of Tumor Cell Populations," Dr. George Klein, professor of tumor biology at Karolinska Institute, Stockholm, Sweden. The Wistar Institute was founded in 1818 as the Wistar Museum. The museum was expanded into a biological research institute in 1892 in consequence of gifts from Gen. Isaac J. Wistar, grand-nephew of the founder. The Wistar Institute of Anatomy and Biology was formally opened in 1894. The original institute building has been completely reconstructed during the past two years to provide new laboratories and a new museum.

TENNESSEE

Grant for Brain Research.—One million dollars for a five-year study on prevention of brain damage has been awarded to the University of Tennessee College of Medicine by the National Institute of Neurological Disease and Blindness, U. S. Public Health Service. Announcement of the largest grant the medical units have ever received was made by Dr. O. W. Hyman, vice-president in charge of the medical units, and Dr. Maston K. Callison, dean of the college. Funds will be available at the rate of more than $200,000 per year. Dr. James G. Hughes, professor of pediatrics, will be principal investigator, and Dr. Phillip C. Schreier, professor of obstetrics and gynecology, co-investigator. The Memphis study will involve close cooperation between several departments in the college. More than 40 people will be on the research team. About 750 women and their babies in units of City of Memphis Hospitals will be studied for five years. The local project is part of a collaborative effort in which 15 medical schools in the nation will participate, simultaneously collecting information on causes of brain damage. Information from the schools will be pooled, and it is expected that by the end of five years the schools will have studied more than 60,000 pregnant women and their offspring.

Annual Meeting in Memphis.—The 124th annual meeting of the Tennessee State Medical Association will be held April 12-15 in Memphis, with headquarters at the Peabody Hotel. Guest speaker at the president's banquet, April 13, 7 p. m., with Dr. James C. Gardner, president, presiding, will be Robert J. Farley, LL.B., dean of the School of Law, University of Mississippi, Oxford. At the General Practice Day session that day, a symposium, "Peripheral Vascular Disease—Its Management," will be moderated by Dr. Harwell Wilson. Special society meetings will be held each day. Papers by out-of-state speakers to be presented at the general sessions are as follows:

The Role of the Anesthesiologist in the Practice of Medicine, Dr. Scott M. Smith, Salt Lake City, Utah.
Antibiotic Resistant Staphylococcic Disease, Dr. William Sandusky, Charlottesville, Va.
The Pathology of Low Back Pain, Dr. Walter C. J. Putschar, Washington, D. C.
Infertility—A Family Unit Problem, Dr. William H. Masters, St. Louis.
The Newer Oral Antidiabetic Agents, Dr. Rachmiel Levine, Chicago.

A second symposium, "Diuretics," is scheduled for the morning of April 14. Scientific and technical exhibits are planned. For information, write the Tennessee State Medical Association, 112 Louise Ave., Nashville 5, Tenn.

TEXAS

Annual State Meeting in San Antonio.—The 92nd annual session of the Texas Medical Association will be held April 18-21 in San Antonio, with headquarters at the Hilton Hotel. Among the papers to be presented are "Abnormal Uterine Bleeding at or After the Menopause," Dr. Newell W. Philpott, Montreal, Canada, professor of obstetrics and gynecology, McGill University Faculty of Medicine, and "Land of the Free and Easy," by Dr. Gunnar Gundersen, La Crosse, Wis., President, American Medical Association. Other guest speakers include the following:

Drs. Walter C. Alvarez and Edward I. Compere, Chicago; George C. Andrews, John M. McLean, and Byron Smith, New York City; Harry E. Bacon and James E. Eckenhoff, Philadelphia; Richard J. Bing, St. Louis; Murray M. Copeland and Oscar B. Hunter Jr., Washington, D. C.; John B. Erich, Rochester, Minn.; Jack R. Ewalt, Donald D. Matson, Duncan E. Reid, and Kenneth W. Warren, Boston; Grace A. Goldsmith, New Orleans; Eugene A. Hargrove, Raleigh, N. C.; Herman E. Hilleboe, Albany, N. Y.; Ted F. Leigh, Atlanta, Ga.; Champ Lyons, Birmingham, Ala.; Mitchell I. Rubin, Buffalo, N. Y.; O. A. Sander, Milwaukee, Wis.; and John T. Sessions Jr., Chapel Hill, N. C.

Section meetings, motion picture sessions, and scientific and technical exhibits are arranged. The annual golf tournament will be held April 20. President of the Texas Medical Association is Dr. Howard O. Smith, Marlin. For information write Mr. C. L. Williston, 1801 N. Lamar Blvd., Austin, Texas, Executive Secretary.

GENERAL

Award for Work on Obstetrics or Gynecology.—The Central Association of Obstetricians and Gynecologists is offering an award of $250 for outstanding investigative or clinical work in obstetrics or gynecology. Any accredited physician, research worker, or medical student living within the geographic confines of the Association is eligible. Papers must be written expressly for this competition and must be original. The winning paper will be presented at the annual meeting Sept. 24-26 in Chicago. Manuscripts should be submitted to the secretary in triplicate, accompanied by an abstract not to exceed 150 words. No author's identification shall be shown on any of the three copies, the only identification being a covering letter addressed to the secretary. Papers should be in the hands of the secretary by June 25 and should be addressed to: Dr. Edwin J. DeCosta, Secretary, Central Association of Obstetricians and Gynecologists, 104 S. Michigan Ave., Suite 615, Chicago 3.

Urological Meeting in Atlantic City.—The 54th annual meeting of the American Urological Association, Inc., will be held April 20-23 at the Chalfonte–Haddon Hall, Atlantic City, N. J., under the presidency of Dr. Adolph A. Kutzmann, Los Angeles, who will present the presidential address the afternoon of April 22. Over 25 papers are scheduled for presentation with discussions following. Dr. Hans J. Klapproth, Cleveland, will present "Distribution of Renal Arterial Circulation in the Dog" the morning of April 21 as the first prize essay contest lecture. A program of motion pictures and scientific and technical exhibits are arranged. The Ramon Guiteras Lecture, "Explants of Genito-Urinary Tissues Cultivated for Experimental Studies," will be given by C. M. Pomerat, director, Tissue Culture Laboratory, University of Texas Medical Branch, Galveston. Panel discussions on "Carcinoma of the Bladder" and "The Prostatic Nodule" are arranged. Dr. Einar Ljunggren, Goteborg, Sweden, will present "Some Aspects of Renal Tumors" the afternoon of April 23.

Experimental Biology Meeting in Atlantic City.—The 43rd annual meeting of the Federation of American Societies for Experimental Biology will be held in Atlantic City, N. J., April 13-17. The federation is comprised of the American Physiological Society, the American Society of Biological Chemists, the American Society for Experimental Pathology, the American Society for Pharmacology and Experimental Therapeutics, the American Institute of Nutrition, and the American Association of Immunologists. Headquarters hotel for the federation will be the Traymore. An opening joint session will be held April 14, 8 p. m., under the title "The Biological Significance of the Fine Structure of Macromolecules," with Dr. Francis H. C. Crick, Cambridge, England, as chairman, and including a paper by Dr. J. C. Kendrew, Cavendish Laboratory, Cambridge, England, on "Structure and Function in Myoglobin and Other Proteins." Intersociety sessions under the titles "Physiology and Drug Actions," "Nutritional Requirements of Animal Cells Cultivated in Vitro," and "Neurochemistry" (two sessions) will include the following section titles: Neurochemistry, Atherosclerosis, Blood Clotting, Tissue Culture, Cytology, Neuropharmacology, and Radiation. A program of motion pictures will be presented April 13. Industrial scientific exhibits are planned.

World Conference on Medical Education.—Plans for the second World Conference on Medical Education, to be held in Chicago Aug. 29-Sept. 4, were discussed recently. The seven-day conference, sponsored jointly by world medical bodies, including the World Medical Association, is arranged "to provide a common ground for the free exchange of scientific information and experiences between countries." Collaborating with the W. M. A. in sponsoring the conference are the World Health Organization, the Council for International Organizations of Medical Sciences, and the International Association of Universities. President Eisenhower, who helped organize the National Fund for Medical Education, is patron of the conference. Serving as conference president will be Dr. Raymond B. Allen, chancellor, University of California, Los Angeles. To be held in the Palmer House, the conference will have 125 speakers from about 50 countries, and all business, including lectures, will be translated simultaneously into English, French, and Spanish. "Medicine—A Lifelong Study" is the conference theme. For information write Mrs. Clara Lewinter, World Medical Association, 10 Columbus Circle, New York 19.

Government Awards for Lecturing and Research.—U. S. Government Awards for 1960-61, authorized by Public Law 584, 79th Congress, The Fulbright Act, under the auspices of the Board of Foreign Scholarships and the Department of State, were announced. These awards are available for university lecturing and for advanced research in Latin America (Argentina, Brazil, Chile, Colombia, Ecuador, Peru); South and Southeast Asia (Burma, India, Pakistan, Philippines, Thailand); and Pacific Area (Australia, New Zealand). Eligibility includes U. S. citizenship; at least one year of college or university teaching experience (for lecturing); a doctoral degree for research or recognized professional standing (candidates for the degree should apply to the Institute of International Education, 1 E. 67th St., New York City); in some cases, a knowledge of the language of the host country. Awards will be tenable in one country, usually for an academic year,

Meeting in Chicago to discuss plans for the second World Conference on Medical Education were (left to right): Dr. W. C. Bornemeier, Chicago; Dr. Glen R. Shepherd, assistant secretary, Council on Medical Education and Hospitals, A. M. A.; Miss Margaret Natwick, executive assistant, W. M. A.; Thomas R. Gardiner, co-chairman of the technical exhibits; Dr. Robert A. Moore, dean, College of Medicine in Brooklyn, State University of New York; Dr. George F. Lull, retired secretary and general manager, A. M. A.; Dr. Myron E. Wegman, secretary general, Pan American Sanitary Bureau; Mrs. Clara Lewinter, executive secretary of the conference; Dr. Victor Johnson, director, Mayo Foundation for Medical Education and Research; and Dr. Louis H. Bauer, Secretary General of the World Medical Association.

and payable in currency of host country. Round-trip travel for the grantee will be provided but not for members of his family. A maintenance allowance to cover ordinary living expenses of the grantee and his family while in residence abroad and a small incidental allowance for travel, books, and services required in performance of assignment will be given. Closing date of application is April 25. For application forms and information write: Conference Board of Associated Research Councils, Committee on International Exchange of Persons, 2101 Constitution Ave., Washington 25, D. C.

Psychiatrists Meet in Philadelphia.—The American Psychiatric Association will hold its 115th annual meeting at Convention Hall Auditorium in Philadelphia April 27-May 1. Dr. Francis J. Gerty, Chicago, president of the association, will call the meeting to order the morning of April 27. Over 160 papers will be presented, including the following by foreign authors:

A Cross-Cultural Approach to Mental Illness, Dr. Eric D. Wittkower and J. Fried, Ph.D., Montreal, Canada.
Further Developments in the Day Hospital, Dr. T. J. Boag, Montreal.
The Practice of Psychiatry in England Under the National Health Service, Dr. A. Spencer Paterson, London.
A Family Programme for First Year Medical Students, Dr. J. S. Tyhurst, Vancouver, British Columbia.
Socio-Economic Factors in Discharge of Long-Term Mental Hospital Patients, Dr. Gordon O. Patton, Quebec, Canada.
Types of Marital Complementarity and Emotional Health of Children, Dr. Nathan B. Epstein and William A. Westley, Ph.D., Quebec.
A Follow-Up Study of Two Groups of Veterans: (a) Five Years (b) Ten Years, Treated with Sub-Coma Insulin at a Montreal Veterans Hospital, Dr. Harry Grauer, Montreal.

Two dozen evening round-table meetings are planned. Dr. Karl A. Menninger, Topeka, Kan., will give the Academic Lecture. The Adolf Meyer Research Lecture will be given by Dr. W. Grey Walter, Bristol, England. For information, write the American Psychiatric Association, 1700 18th St., N. W., Washington 9, D. C.

Meeting of Physicians in Chicago.—The American College of Physicians will meet April 20-24, with headquarters at The Conrad Hilton Hotel, Chicago, Dr. Eliot E. Foltz of Winnetka, Ill., general chairman, announced. The presentation will include more than 100 papers, 23 panels, clinics at 13 hospitals, 6 clinical-basic science case conferences, 12 color television clinics, 31 clinical investigation reports, 18 scientific exhibits, and a technical exhibit. In the morning, two-hour clinics will be held in the hospitals, followed by panels in the hotel and in the Blackstone and Eighth Street Theaters. At the same time, clinical-basic science case reports will be held in the hotel. A new feature will be a public meeting to which business, civic, and nonmedical professional leaders will be invited. A panel will discuss "The Care and Preservation of the American Executive." The panelists will be Drs. Philip S. Hench, Henry L. Bockus, William C. Menninger, Chester M. Jones, Sara M. Jordan, Howard P. Lewis, Irvine H. Page, and Walter L. Palmer. Dr. Dwight L. Wilbur, of San Francisco, president of the college, will be moderator. The annual business meeting will be held April 23. Officers, regents, and governors will be elected. Dr. Howard P. Lewis, of Portland, Ore., will be inducted as president to succeed Dr. Wilbur. The annual convocation, will be held the evening of April 22, and will include an address by Dr. Wilbur. For information, write Mr. E. R. Loveland, Executive Director, The American College of Physicians, 4200 Pine St., Philadelphia 4.

International Committee on Aging Problems.—An International committee to exchange with foreign countries information about health and welfare programs for older people was established by the National Committee on the Aging. Chairman of the international committee is Dr. Michael M. Dacso, director, physical medicine and rehabilitation, Goldwater Memorial Hospital, New York City. The committee's first task will be to exchange information and experience with leaders of health and welfare programs for older people in Europe and Asia. The National Committee on the Aging, a standing committee of the National Social Welfare Assembly, is a national resource for planning, information and consultation in the field of aging. It is a nonprofit organization.

FOREIGN

Veterinary Congress in Madrid.—The 16th International Veterinary Congress will be held May 21-27 in Madrid, Spain, at the Faculty of Medicine, University City. Two general subjects are planned: "Social Mission of the Veterinary Science and Practice" and "Nuclear Energy and Veterinary Sciences." Section titles are as follows:

Veterinary Medicine.
Epizootology.
Veterinary Public Health.
Zootechnics.
Veterinary Profession.

A program of films, excursions, receptions, and a ladies' program are planned. The official languages will be Spanish, French, English, and German, and simultaneous translation will be provided. For information write the 16th International Veterinary Congress, 11, Villanueva Street, Madrid, Spain.

Symposium on Bacterial Resistance.—On May 1-3 a symposium on the Prevention of Bacterial Resistance to Antibiotics in Obstetrics and Gynecology will be held in Perugia, Italy, sponsored by the Italian Society of Obsterics and Gynecology. The symposium, to be held at the University of Perugia, will have the following session titles:

Problems Relating to Bacterial Resistance in a Maternity Hospital.
(a) Resistant organisms in the wards of an obstetrical and gynecological service.

(b) The problem of bacterial resistance and infections in obstetrics and gynecology.

Suggestions for the Prevention of Bacterial Resistance.

(a) Extension and limitations in the prophylactic use of antibiotics and chemotherapeutics (operative vaginal deliveries, caesarian sections, infected abortions and labors, gynecological operation, etc.).

(b) Reserved antibiotics in safe-keeping. Their use in emergency cases.

(c) Nonantibiotics and analogous drugs as prophylactic and therapeutical agents in infected cases in obstetrics and gynecology.

Conclusions.

No fees are required for registration. Simultaneous interpretations will be provided in Italian and English, and proceedings will be recorded for publication. A ladies' program and entertainment schedule are planned. Correspondence should be addressed to: Segreteria del Simposio, Clinica Ostetrics e Ginecologica dell'Università, Policlinico, Perugia, Italy.

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* Various locations, July 8, 1960. Final date for filing application is January 8. Sec., Dr. Forrest E. Leffingwell, 217 Farmington Ave., Hartford 5, Conn.

AMERICAN BOARD OF DERMATOLOGY: *Written.* Several Cities, Oct. 5. *Oral.* Oklahoma City, Jan. 15-18, 1960. The final date for filing all applications is July 1, 1959. Sec., Dr. Beatrice M. Kesten, One Haven Ave., New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *1959 Schedule—Written,* Oct. 19. Final date for filing application is May 1. *Oral.* For candidates in the Midwest. Chicago, April 15-18. Final date for filing application was Jan. 1. *Oral.* For candidates on the West Coast. Final date for filing application was March 1. *Oral.* For candidates on the East Coast, Nov. 6-7, 9-10. Final date for filing application was March 1. *Examination in the Subspecialties. Gastroenterology.* Philadelphia, April 17-18. Final date for filing application was Feb. 1. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Leonard T. Furlow, Washington University School of Medicine, St. Louis 10.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *I. Oral and Clinical.* Chicago, May 8-19. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates. Candidates who participated in the Part I examinations will be notified of their eligibility for the Part II examinations as soon as possible. Deadline for receipt of new and reopened application for the 1960 examinations is Aug. 1, 1959. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral.* Philadelphia, June 2-6; St. Louis, Oct. 6-10. *Written.* January 1960 in various cities. Applications for the 1960 written examination must be filed before July 1. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Part II.* Chicago, Jan. 19-21, 1960. The deadline for the receipt of application is Aug. 15, 1959. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Oral.* Chicago, Oct. 5-9. Final date for filing application is April 1. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PATHOLOGY: Boston, April 16-19. Final date for filing application was Feb. 28. Sec., Dr. Edward B. Smith, 1100 W. Michigan St., Indianapolis 7.

AMERICAN BOARD OF PEDIATRICS: *Written.* January 1960. Exec. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION: *Written, Part I,* and *Oral, Part II.* Philadelphia, June 12-13. Final date for filing application was February 15. Sec., Dr. Earl C. Elkins, 200 First St., S. W., Rochester, Minn.

AMERICAN BOARD OF PLASTIC SURGERY: *Oral and Written.* Miami, Fla., Oct. 15-17. Final date for submitting case reports is July 1. Corresponding Secretary, Miss Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8, Mo.

AMERICAN BOARD OF PREVENTIVE MEDICINE: *Public Health.* Minneapolis, Boston, Baltimore, Chapel Hill, North Carolina and New Orleans, April 9-11; Berkeley, Calif., April 23-25; Pittsburgh, April 16-18. *Occupational Medicine.* Chicago, April 24-26. *Aviation Medicine.* Los Angeles, April 24-26. Final date for filing all applications is March 16. Sec., Dr. Tom F. Whayne, 3438 Walnut St., Philadelphia 4.

AMERICAN BOARD OF PROCTOLOGY: *Oral and Written.* Philadelphia, September. Final date for filing application is March 15. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New Orleans, Mar. 16-17; Chicago, Oct. 19-20; New York, Dec. 14-15. Training credit for full time psychiatric and/or neurologic assignment in unapproved military programs or services between the dates of Jan. 1, 1950 and Jan. 1, 1954 was terminated on Jan. 1, 1959. Sec., Dr. David A. Boyd, 102-110 Second Ave. S. W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: *Examination.* Chicago, June 2-4. If needed a special examination will be offered at this time in Nuclear Medicine to diplomates in Radiology or Therapeutic Radiology. The deadline for filing applications is April 1. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Written* examinations (Part I) will be held on December 2, 1959 at various centers to be announced later. Candidates are urged to apply several months before completion of training requirements although the closing date for filing applications is August 1. Those completing training requirements after September 30 cannot be considered for the Part I examination in December of the same year. *Part II.* San Francisco, April 13-14; Indianapolis, May 11-12; Columbus, Ohio, May 14-15. Sec., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

BOARD OF THORACIC SURGERY: *Written.* Various centers throughout the country, September 1959. Final date for filing application is July 1. *Oral.* September. Final date for filing application is July 1. Sec., Dr. William M. Tuttle, 1151 Taylor Ave., Detroit 2, Mich.

AMERICAN BOARD OF UROLOGY: *Written.* Approximately 25 cities throughout the country, December 4, 1959. *Oral-Clinical* and *Examination in Pathology.* Chicago, February 1960. Final date for filing application is Sept. 1, 1959. Sec., Dr. William Niles Wishard, 30 Westwood Rd., Minneapolis 26, Minn.

GOVERNMENT SERVICES

ARMY

Personal.—Brig. Gen. Perrin H. Long of Brooklyn, N. Y., has transferred to the Retired Reserve. He began his military career in the ranks during World War I. After receiving a direct appointment as lieutenant colonel in August, 1942, he served on active duty in North Africa and Europe as a medical consultant. He completed more than 18 years of active and reserve service; his last assignment prior to retiring was mobilization designee as a special assistant to the Surgeon General.

NAVY

Film Certificate Awarded.—The Navy received an Edinburgh International Film Festival certificate for a Bureau of Medicine and Surgery film entitled "Color Vision Deficiencies." The certificate was presented by British Ambassador Sir Harold Caccia in March. The Edinburgh Festival is an annual event. Over a period of 15 years, the Navy has been given about 34 national and international awards for its motion pictures. "Color Vision Deficiencies" (MN 8246) is a 16-mm. color film with sound. The running time is 20 minutes. It is intended for medical department personnel who are responsible for color vision tests.

Captain Shone Elected.—Capt. Lloyd B. Shone, Medical Corps, U. S. Navy, was elected secretary of the American Academy of Occupational Medicine at the Academy's 11th Annual Meeting in Boston in February. He is presently director of the Occupational Medicine and Dispensary Division in the Bureau of Medicine and Surgery and is certified as a specialist in occupational medicine by the American Board of Preventive Medicine.

VETERANS ADMINISTRATION

Dr. Middleton Reappointed.—Dr. William S. Middleton was reappointed for a second four-year term as chief medical director of the Veterans Administration. As VA chief medical director, he heads the agency's 171 hospitals, nearly 100 outpatient clinics, and nationwide hometown medical services, which together provide care for about 2,500,000 patients yearly.

PUBLIC HEALTH SERVICE

Embryology Committee.—An experimental Embryology and Development Training Committee was appointed by the surgeon general. It held its first meeting at the Harvard Medical School in February. Under the chairmanship of Dr. Louis Bellman, professor and chairman of obstetrics and gynecology at the State University of the New York School of Medicine, the committee will review training grant applications in experimental embryology and related basic sciences. It will function under Dr. G. Halsey Hunt, chief of the division of general medical sciences, and Dr. Frederick L. Stone, assistant division chief and chief of the research training branch. Dr. Howard P. Jenerick will be executive secretary. The work of the committee, which is made up of members representing many of the basic specialties related to human reproduction and development, will help meet the increasing need for emphasis on research training in these fields. The program will support research training for postresidents or other postdoctoral and predoctoral trainees in electron microscopy, genetics, developmental physiology, neonatal pathology, fetal biochemistry, and other related basic science fields. In addition to Dr. Hellman, members of the committee include Drs. Robert A. Aldrich, University of Washington School of Medicine, Seattle; Harry H. Gordan, Sinai Hospital, Baltimore; Duncan E. Reid, Boston Lying-in Hospital, Boston; Howard C. Taylor, Columbia-Presbyterian Medical Center, New York; and James G. Wilson, University of Florida College of Medicine, Gainesville, Fla.

Training in Epidemiology.—A course in applied epidemiology will be offered at the Communicable Disease Center in Atlanta, Ga., May 4-8, 1959, as a part of the continuing program of the center's training branch. This course is designed primarily for physicians who serve as investigators of disease outbreaks or have administrative responsibility for such investigations. It serves both as a refresher course for the experienced health administrators and as an introductory course for physicians new to public health. Emphasis is placed on developing and understanding of how epidemiologic techniques can be used in the approach to the solutions of problems in the preventable disease field. Lecture-discussion sessions and audiovisual aids are used in the presentations, but emphasis is placed on group participation, which is obtained through group solution of epidemiologic problems, seminar-type presentations, and panel discussions. Registrants will be expected to attend all sessions of the course. Further information and application forms may be obtained from: Chief, Communicable Disease Center, Public Health Service, 50 Seventh St. N. E., Atlanta 23, Ga., Attention: Chief, Training Branch.

DEATHS

Owen, Abraham Miconias Ⓜ Bloomington, Ind.; Indiana University School of Medicine, Indianapolis, 1940; veteran of World War II; associated with Bloomington Hospital; died Jan. 12, aged 58.

Pennell, Samuel, Brooklyn; Cornell University Medical College, New York City, 1926; veteran of World War II; on the staffs of the Jewish and Maimonides hospitals; specialist certified by the American Board of Pathology; died Jan. 1, aged 58.

Potter, Joseph Lumbard Ⓜ Duke Center, Pa.; Medico-Chirurgical College of Philadelphia, 1916; died Dec. 22, aged 65.

Rogers, Charles Lewis Ⓜ Norman, Okla. (licensed in Oklahoma by years of practice); died in a hospital at Bartlesville Jan. 26, aged 82.

Rose, Joseph Everett Ⓜ Pensacola, Fla.; University of Alabama School of Medicine, Mobile, 1909; died Dec. 28, aged 79.

Scott, James Stanley, Pomona, Calif.; University Medical College of Kansas City, Mo., 1896; died Dec. 17, aged 92.

Shipper, Philip Marvin, New York City; Indiana University School of Medicine, Indianapolis, 1934; served on the staffs of the Cornell Medical Center–New York Hospital and Beth David Hospital; died in the New Rochelle (N. Y.) Hospital Dec. 24, aged 48.

Siminson, Irwin Dave Ⓜ Mineral Point, Wis.; Rush Medical College, Chicago, 1924; for many years practiced in Chicago, where he was on the staff of the Mercy Hospital and chief surgeon with the New York Central Railroad; died Jan. 26, aged 63.

Skinner, James Edwards, Tacoma, Wash.; Rush Medical College, Chicago, 1896; for many years a medical missionary in China; died in Battle Ground Jan. 12, aged 91.

Sonnenschein, Joseph Benjamin Ⓜ Chicago; Rush Medical College, Chicago, 1902; veteran of World War I; for many years connected with the city board of health; died in the Chicago Wesley Memorial Hospital Jan. 30, aged 82.

Stalker, John Morton, Borden, Ind.; University of Louisville (Ky.) Medical Department, 1906; served as trustee of the Borden Schools; on Thanksgiving Day in 1957 Borden proclaimed "Dr. Stalker Day" at the Borden High School; died Jan. 10, aged 76.

Staples, Mary Morrison, San Francisco; University of California School of Medicine, San Francisco, 1894; died Jan. 14, aged 98.

Stapp, Roth Van Allen, Houston, Texas; St. Louis University School of Medicine, 1930; veteran of World War II; died Jan. 19, aged 53.

Stevenson, Holland Newton Ⓜ Pelham, N. Y.; born in Pittsfield, Mass., in 1886; Johns Hopkins University School of Medicine, Baltimore, 1912; specialist certified by the American Board of Otolaryngology; member of the American Laryngological, Rhinological and Otological Society; fellow of the American College of Surgeons; formerly on the faculty of his alma mater, Columbia University College of Physicians and Surgeons in New York City, Creighton University School of Medicine in Omaha and at the New York Post-Graduate Medical School and Hospital in New York City; associated with the New Rochelle (N. Y.) Hospital; a director of the National Bank of Westchester; died Jan. 11, aged 72.

Swart, William Sheridan Ⓜ Girard, Kan.; Barnes Medical College, St. Louis, 1899; died Dec. 19, aged 83.

Swenson, Henning Melville Ⓜ Chicago; University of Illinois College of Medicine, Chicago, 1929; veteran of World War I; on the staff of the Augustana Hospital for many years; died Jan. 17, aged 58.

Taubenhaus, Matthew Ⓜ Chicago; born in Warsaw, Poland, Nov. 29, 1903; Medizinische Fakultät der Universität, Vienna, Austria, 1928; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the Endocrine Society, Chicago Society of Internal Medicine, Society of Experimental Biology and Medicine, American Diabetes Association, New York Academy of Sciences, and the American Association for the Advancement of Science; in 1952 a Claude Bernard visiting professor at the University of Montreal; in March, 1939, came to the United States and began his association with Michael Reese Hospital; first in the department of metabolic and endocrine research and then in the department of medicine; at the time of his death, was attending physician at the hospital and vice-chairman of the department of medicine; died Jan. 16, aged 55.

Ⓜ Indicates Member of the American Medical Association.

Traweek, Albert Carroll Sr. Ⓜ Matador, Texas; Fort Worth School of Medicine, Medical Department of Fort Worth University, 1901; member of the American Academy of General Practice; for many years county health officer; superintendent of the Traweek Hospital, of which he was the owner; died in the Quanah (Texas) Memorial Hospital Jan. 10, aged 83.

Troncoso, Manuel Uribe Ⓜ New York City; born June 17, 1867; Universidad Nacional Facultad de Medicina Mexico, D. F., 1890; specialist certified by the American Board of Ophthalmology; served as professor of ophthalmology at the New York Post-Graduate Medical School and Hospital and assistant professor of clinical ophthalmology at the Columbia University College of Physicians and Surgeons; in 1942 received the research medal of the American Medical Association Section on Ophthalmology; author of "A Treatise on Gonioscopy"; wrote "Internal Diseases of the Eye and Atlas of Ophthalmoscopy," which has gone through many editions; died in the Frances Schervier Home and Hospital Jan. 21, aged 91.

Underwood, Felix Joel Ⓜ Jackson, Miss.; born in Nettleton, Nov. 21, 1882; Memphis (Tenn.) Hospital Medical College, 1908; began his public health career in 1918 as health officer for Monroe County and served until 1921; in the latter year came to Jackson and became director of the Bureau of Child Hygiene for the Mississippi State Board of Health, serving until 1924, when he became executive officer and secretary and held that post until his retirement in June, 1958; served as president of the American Public Health Association; twice was the recipient of the Lasker Award; received it first in 1945 for his planned parenthood program, and again in 1953 for outstanding public health administration; in 1941 president of the Southern Branch of the American Public Health Association and served as chairman of the regional executive board and member of the governing council; past-president of the Southern Medical Association, Mississippi Public Health Association, Conference of State and Provincial Health Authorities of North America, Mississippi State Medical Association, State Conference of Social Work, and the State Board of Examiners for Nurses; from 1912 to 1925 secretary of the Northern Mississippi Thirteen Counties Medical Society; director at large, National Tuberculosis Association from 1942 to 1944; served as a member of the board of directors of the American Cancer Society and recipient of a plaque as an award for meritorious service as campaigning chairman for the state division in 1948; member of the House of Delegates of the American Medical Association from 1933 to 1946 and from 1949 to 1951; general chairman of the Mississippi Council for Child Health and Protection; member of the State Board of Public Welfare from 1933 to 1935; delegate to several congresses and conferences; specialist certified by the American Board of Preventive Medicine, of which he served as vice-chairman; associate in public health, University of Mississippi School of Medicine; guest lecturer, Tulane University in New Orleans and Meharry Medical College in Nashville, Tenn.; special consultant to the surgeon general, U. S. Public Health Service, and to the National Advisory Mental Health Council; fellow of the American College of Physicians; for three years served as a member of the board of scientific directors of the Rockefeller Foundation in New York City; for many years member of the board of directors of the Standard Life Insurance Company; member of the staffs of the Mississippi Baptist, St. Dominic, and Mississippi State Charity hospitals; secretary of the board of trustees of the Mississippi State Tuberculosis Sanatorium; member of the state commission on hospital care; member and past-president of the board of trustees of the Mississippi Children's Home Society; for many years state fund raising chairman of the National Foundation for Infantile Paralysis; also served in an executive capacity for numerous other community and health organizations; a state building was named in his honor; in 1950 received the Arthur T. McCormack Award; in the last three weeks of his life, received two top accolades for service to his state; United Press International newspaper, TV, and radio editors named him "1958 Man of the Year"; winner of the new University of Mississippi–First Federal Foundation "Missy" award for distinguished service; the *Mississippi Doctor* for September, 1944, was designated the Underwood issue in his honor; the journal carried many tributes for him and a review of the health of the state under his direction; joint author of "History of Public Health and Medical Licensure," Vol. I, 1798-1937, Vol. II, 1938-1947; died Jan. 9, aged 76.

Vander Veer, Albert Ⓜ Charlotte, N. C.; Columbia University College of Physicians and Surgeons, New York City, 1904; specialist certified by the American Board of Internal Medicine; practiced in New York City for many years and was associated with the Roosevelt Hospital; veteran of World War I; past-president of the American Academy of Allergy; died in the Presbyterian Hospital Jan. 31, aged 79.

Vorpahl, Rudolph Augustus Ⓜ Cedar Rapids, Iowa; Milwaukee Medical College, 1905; veteran of World War I; for many years county coroner; died Jan. 14, aged 78.

FOREIGN LETTERS

AUSTRIA

Icterus Neonatorum.—At the meeting of the Society of Physicians in Vienna on Jan. 30, Dr. H. Gross stated that the most important form of icterus in the newborn infant is the icterus gravis associated with erythroblastosis fetalis. Patients with this type of icterus must be given exchange blood transfusions to prevent early death or permanent damage because of kernicterus resulting from hyperbilirubinemia. Other diseases to be considered in the differential diagnosis include epidemic hepatitis; the rare homologous serum hepatitis; congenital cirrhosis of the liver; acute yellow atrophy; occlusion of bile ducts by aplasia, artresia, stenosis due to choledochus cysts or adhesions, or thickened bile; general sepsis; congenital syphilis; toxoplasmosis; cytomegaly; listeriosis; occasionally diabetes mellitus, a prediabetic condition of the mother or a toxemia of pregnancy; and rarely cystic fibrosis of the pancreas. Administration of large doses of vitamin K may also lead to hyperbilirubinemia. One may observe a prolonged icterus also in children with congenital thyroid deficiency. In addition a severe, long-continued icterus frequently occurs in premature infants and is due to a functional immaturity of the liver. Exchange blood transfusions may be considered for the prevention of kernicterus in patients with a rise of the indirect bilirubin serum level to more than 20 mg. per 100 cc.

Pheochromocytoma.—At the meeting of the Society of Physicians in Vienna, on Jan. 6, Drs. O. Kraupp and H. Bernheimer stated that a greatly increased excretion of pyrocatechin is pathognomonic of a pheochromocytoma. A slightly increased renal excretion of epinephrine does not, however, rule out the presence of a chromaffin tumor. The speakers confirmed the diagnostic significance of the 3-methoxy-4-hydroxymandelic acid excreted in the urine of a patient with a tumor secreting levarterenol and epinephrine. The symptoms disappeared and the amount of pyrocatechin excretion, which was high in the beginning of observation, dropped within a few weeks; but the 24-hour excretion of the mandelic acid derivative remained high and assured the diagnosis of pheochromocytoma. In this case the *p*- and m-hydroxyhippuric acid excretion was also greatly increased. After excision of the tumor the excretion of the abovementioned acids decreased to normal. The speakers hoped that by determining the renal excretion of the decomposition products of pyrocatechin the differential diagnosis of a suspected chromaffin tumor would be improved.

The items in these letters are contributed by regular correspondents in the various foreign countries.

BRAZIL

Postoperative Sodium and Potassium Metabolism.—Dr. J. de Moraes and co-workers, of the Rio de Janeiro Hospital São Miguel, (*Rev. brasil. cir.* **36**:137, 1958) studied the metabolism of sodium and potassium in 20 patients, 18 of whom had had gastrointestinal operations and 2 of whom had had operations on the respiratory tract. Water, sodium chloride, and potassium balance studies were made on all patients for eight days, as well as determinations of electrolytes in the plasma on the first, third, and fifth postoperative days. The authors concluded that in the immediate postoperative period there is a low output of sodium in the urine with paradoxical low level of plasma sodium. In this period sodium must be given carefully and the extrarenal salt loss through vomiting, fistulas, and gastric and jejunal aspiration should be compensated in accordance with the amount lost.

When the urinary sodium retention and the hyponatremia last for more than eight days, in spite of adequate replacement, operative complications should be looked for and treated, instead of concentrating on the hyponatremia. An increased output of urinary potassium in the immediate postoperative period and discreet hypopotassemia during the third and fifth postoperative days were observed. This increase in potassium excretion is due in part to the adrenergic corticoid phase. In patients who have taken nothing by mouth for five or more days there may be a depletion of potassium with evident symptoms, abnormalities in the electrocardiogram, and, less frequently, hypopotassemia. If a long period of no oral intake is foreseen, the administration of potassium should be started from the first day, to avoid depletion. In dehydrated patients the potassium replacement must be preceded by rehydration to insure a good output of urine.

Cyanosis in Schistosomiasis.—Dr. J. V. Barbas and co-workers, at a meeting of the Associação Paulista de Medicina reported a case of hepatosplenic schistosomiasis due to Schistosoma mansoni in which the patient showed, during the last part of his illness, dyspnea on exertion and an intense and progressive cyanosis. Physical examination of the lungs, roentgenograms of the chest, and an electrocardiogram

showed no abnormalities. Functional tests of the lungs suggested the presence of a pulmonary arteriovenous fistula. This was confirmed by angiocardiography. Cardiac catheterization showed normal pressure in the pulmonary artery and an increased cardiac output. The pulmonary biopsy specimen showed the presence of schistosomes and of several fistulas between the small branches of the pulmonary artery and the pulmonary veins. These fistulas were caused, as demonstrated in a previous investigation by one of the authors, by schistosome ova. The dyspnea and cyanosis were caused by these arteriovenous microfistulas. The authors believed this to be the first reported case of pulmonary schistosomiasis in which, in the absence of cor pulmonale diagnosed during the life of the patient, marked cyanosis was present in addition to the usual symptoms of hepatosplenic schistosomiasis.

Blastomycosis.—Dr. R. M. Castro and co-workers of the São Paulo State University Hospital (*Rev. paulista med.* **53**:479, 1958) drew attention to the great difficulties of the diagnosis in some patients with Brazilian blastomycosis and illustrated the problem with the report of eight typical cases. As a rule, this disease does not present diagnostic difficulties, as its two common forms—the mucocutaneous and the lymphaticovisceral—present pathognomonic signs and their lesions abound in Blastomyces brasiliensis. Difficulties arise, however, when the process remains restricted to the lymph nodes without a tendency to softening and fistulization or because localized in deep organs without tegumentary manifestation, or when the tegumentary lesion is so small that it escapes discovery. Without the demonstration of the parasite, and the lesions clearly simulating those of other diseases, the diagnosis is sometimes difficult. Of the eight cases presenting diagnostic difficulties two resembled Hodgkin's disease and the diagnosis was established only after lymph node biopsy; three which could be classified as an icteric form had a bout of obstructive jaundice caused by compression of the biliary ducts by masses of enlarged lymph nodes and the diagnosis was made at operation; one simulating a severe hemopathy was diagnosed only at autopsy; one died before a diagnosis could be made and was diagnosed at autopsy; and one simulating adrenocortical hypofunction also could be diagnosed only at autopsy.

An early and accurate diagnosis is of the utmost importance because specific treatment can now cure what is otherwise a highly fatal disease. Aside from identification of the causative organism, laboratory tests are of little value. Hyperglobulinemia, however, suggests a granulomatous process. This may give a valuable clue in cases simulating a neoplastic or leukemic process, since in those conditions hyperglobulinemia does not occur.

FINLAND

The Training of Specialists.—Last summer representatives of the Scandinavian Medical Associations met in Ulvik to discuss, among other things, postgraduate study and the training of specialists. Dr. Kosonen, of Finland, pointed out that before 1932 no organization had had authority to confer on physicians the title of specialist. Since then the committee created by the Finnish Medical Association for this purpose has issued rules which have needed revision from time to time so as to reflect the most recent experiences in this sphere. By now there are 37 fields in which a physician may qualify as a specialist, but there are only 14 main specialties. Broadly speaking, the specialist must have a year of ordinary postgraduate training plus three years of some special subject studied at a teaching hospital. Hitherto he has not been required to pass any special examination on his specialty, and his qualifications have not been scrutinized by any disciplinary body. Of late there has been a controversy over the creation of a new board of examiners of candidates for the title of specialist, with the public health authorities, the medical faculties, and the Finnish Medical Association pulling in different directions. Dr. Kosonen would like to see the standards of specialty training in Finland brought closer to the level of the other Scandinavian countries. For the present this would require study in medical centers outside Finland.

Pediatric Surgery.—Dr. M. Sulamaa, of the Helsinki Childrens Clinic, recommended that operations on children be performed in a children's rather than a general hospital (*Nordisk medicin*, Dec. 18, 1958). His study for the period 1947 to 1957 includes a wide range of cases which he classes as general, septic, urologic, thoracic, orthopedic, or neurological surgery and tumors. In each of these spheres he would like to see the development of pediatric surgery always within the framework of a children's hospital. Even the surgical instruments of a children's hospital are distinctive, witness the special characteristics of the outfit for intravenous injections. There are also special requirements for the feeding and washing of children, all much different from the corresponding requirements for adults.

Conditions in Lapland.—In 1956 a series of field studies of intestinal infections in a part of Finnish Lapland with a population of about 5,500 was made. Aided by the Department of Epidemiology of the Harvard School of Public Health, this team issued a report (*Nordisk medicin*, Jan. 22, 1959) which gives an illuminating picture of social conditions peculiar to this part of Finland. The ravages of World War II were so great that practically all the houses in the area in question were new. These

houses, built since 1944, provide an anteroom or even two such rooms in succession so as to keep the main living room comparatively warm. A living room opening directly onto the outer world is now rare. Owing to great distances from school, many children have to live in boarding houses during the school term. Milk is not pasteurized and it passes from the producer direct to the consumer in most cases. When there is an intermediate agent, care is taken to keep the various supplies separate to avoid wholesale mixing. The slaughtering of reindeer is limited to the winter when the meat is kept frozen by natural means. Meat required for consumption in the summer is lightly salted and then smoked and dried in the winter. Here, again, the middleman is usually avoided, the householder either producing his own meat or getting it from his neighbor. Fresh meat is not eaten in the summer when fish becomes the householder's staple diet, much enriched toward the end of the summer by fruit and vegetables. Thanks in large part to the customary weekly steam bath, the personal cleanliness of this community is noteworthy.

INDIA

Alcaligenes Faecalis.—Sarkar and Tribedi (*Indian Journal of Medical Sciences*, vol. 12, December, 1958) stated that Alcaligenes faecalis, although described as a normal inhabitant of the intestinal tract, has also been reported by many workers to be the cause of enteric-like fever, meningitis, cystitis, abscesses, appendicitis, arthritis, and other conditions. For this reason all the strains of A. faecalis isolated from pathological material (blood, urine, feces, pus, and spinal fluid) received from different wards were studied by the authors. The feces of normal healthy persons and the feces of patients convalescing from acute diarrhea, dysentery, cholera, and typhoid were also cultured. All the strains were grown in special mediums to distinguish soil-forms of this organism from the intestinal type. Swabs from hands of house staffs and nurses and from the skin of the antecubital fossae of patients with a blood culture positive for A. faecalis were also cultured. Animal pathogenicity tests were made by injecting guinea pigs, rabbits, and mice by different routes with this organism, with or without mucin.

Previous immunization had been accomplished in some cases. Antibody response in patients from whose blood the organism was isolated was also found, blood from normal persons being used as a control. Of 1,960 consecutive blood cultures in a period of three years, A. faecalis was isolated from 93 patients, in 71 of whom the symptoms resembled those of typhoid, and in 14, atypical typhoid with remittent or intermittent fever. Two patients had puerperal fever, two had high fever late in pregnancy, one had fever following abortion, and three had subacute bacterial endocarditis. A. faecalis was isolated from 58 urine samples showing albumin and pus. During the period of study three patients had meningitis, two had abscess, one had pericardial effusion, one had pleural effusion, and one had cervicitis, all yielding A. faecalis on culture. The agglutinin titer could be determined in 32 patients with enteric-like fever whose blood cultures were positive for A. faecalis. Results of the Widal tests were negative in 9; the titer varied from 1:50 to 1:1,250 in 10; and in 13 it was below 1:50. The culture of swabs from the hands of nurses and house staff was uniformly negative, as were the cultures from the skin of antecubital fossae.

A. faecalis was isolated from 2 of 60 stools from healthy persons, 6 of 30 stools from patients convalescing from typhoid, 4 of 12 convalescing from dysentery, and 30 of 120 convalescing from cholera. By growing the strains in the synthetic mediums most of them could be identified as of fecal rather than soil origin. Animal pathogenicity tests showed the organism to be definitely pathogenic in mice when injected with mucin. When injected in an isolated intestinal loop of a rabbit, many strains were revealed to be pathogenic. In none of the patients in this series could a second organism be isolated from any pathological material. Immunizing injections produced protective antibodies in mice, supporting the pathogenic nature of this organism. All the strains, however, are not pathogenic and the virulence is not high. A high agglutinin titer is not a prominent feature of this infection, although 23 of the 32 patients so tested showed an antibody response. The organism could be isolated from the stools of only 2 of the 60 normal subjects, thus throwing doubt on its status as a normal intestinal inhabitant. Its incidence was, however, found to increase in intestinal disorders such as dysentery, acute diarrhea, and cholera. Most of the reported infections with A. faecalis have been from the tropics and subtropics. The authors believe that it probably plays a pathogenic role in these places and, when isolated from pathological material, should be considered as such and not just dismissed as a contaminant.

Gastroenteritis in Children.—Manchanda and Arora (*Indian Journal of Paediatrics*, vol. 25, November, 1958) analyzed a series of 665 cases of acute diarrhea in young children with regard to cause. Of 4,438 patients admitted during the two and one-half year period of study 665 (15%) had acute diarrhea. Of these 77.4% were in the first year of life. In this series 109 (16.4%) died, of whom 79 (15.3%) were below the age of 1 year. More than half the cases developed in the summer months. The mortality among bottle-fed infants was 21.3% compared to 9.18% among breast-fed babies; 424 patients came from poorer families with unsatisfactory housing conditions. Evidence of infection was present at the time of admission in 140 patients—66 had tonsillitis and pharyngitis, 30 had

acute upper respiratory infections, 15 had a discharging ear, 14 had bronchopneumonia, 8 had multiple boils, and 7 had blepharitis. A history of previous attacks of gastroenteritis was obtained in 109, and a history of acute episodes of diarrhea in other siblings in the family was obtained in 72 cases. Stools were examined bacteriologically in only 50 cases. Serologic types of Escherichia coli 055 and 0111 were present in 30% of the specimens. A total of 84 strains were isolated from the stool specimens studied. Besides Esch. coli, other bacteria isolated were Paracolobactrum coliforme, 31.6%; Staphylococcus pyogenes var. aureus, 21.6%; Pseudomonas aeruginosa, 13.3%; and Shigella flexneri, 1.2%. In most stools more than one organism was isolated, pure growth of a single organism being found only rarely.

The incidence of toxemia, severity of the disease, and mortality rates were higher in patients excreting Proteus vulgaris, Ps. aeruginosa, and Staph. pyogenes var. aureus. Thus the mortality from Ps. aeruginosa infection was 66.7%; that from P. vulgaris infection was 37.5%; and that from Staph. pyogenes var. aureus infection was 26%. Esch. coli 0111 was found in three patients under the age of three months (one died), in two between the ages of three and six months, and in one over six months. Esch. coli 055 was isolated in six patients under the age of three months (one died) and in five between three and six months (one died).

All 665 patients were admitted as emergencies, having proved refractory to treatment outside; 384 had vomiting, 93 had blood and mucus in the stools, and dehydration of varying degrees was present in 505. Fluids were given intravenously to 490 and subcutaneously aided by hyaluronidase in 15. These fluids included dextrose solution, plasma, and whole blood. Saline solution was given if vomiting was excessive. Potassium chloride or citrate was added when dehydration was sufficiently overcome and the child started passing urine. Some patients also received calcium gluconate and multivitamin preparations parenterally. Various drugs such as sulfaguanidine, sulfasuccidine, streptomycin, chloramphenicol, chlortetracycline, and various combinations of antibiotics were given.

Blood Histamine in Adults.—Basu and Bhattacharya (*Indian Journal of Medical Sciences*, vol. 12, December, 1958) stated that in certain diseases, histamine is believed to be endogenously liberated, leading to variations in the blood level. It is therefore necessary to know the normal range of blood histamine before such pathological conditions can be distinguished from the normal variations. The authors estimated the blood histamine level of 25 healthy adults, excluding anyone with a history of cutaneous, nasal, or respiratory allergy. Estimations of hemoglobin concentration, total erythrocytes, and total leukocytes, and the absolute eosinophil count were also made. The normal range of blood histamine was found to vary from 1.0 to 6.2 mcg. per 100 ml. of whole blood, with a mean value of 3.8. The absolute eosinophil count ranged from 50 to 450 per cubic millimeter. There was no correlation between the blood histamine level and the absolute eosinophil count. These figures resembled those obtained by workers in other countries, although the highest range observed here is a little lower than that obtained by others.

Expansion of Health Services.—An indication of the standard of national health before India achieved independence could be estimated from the life expectancy of men and women, which was 26.9 years and 26.6 years, respectively, for the decade ending in 1930 and 32.5 and 31.7 years for the decade ending in 1950. Lack of medical facilities, technical personnel, and water supply were among the factors that contributed to this state of affairs. Inadequate financial resources further aggravated the situation. The first Five Year Plan allotted priorities to rebuilding the nation's health and laid the foundation for further progress. The Second Plan envisages bringing health services within the reach of all people. The specific objectives under the Second Plan are establishment of institutional facilities to serve as bases from which health services can be extended, training of technical manpower, control of communicable diseases, campaign for environmental sanitation, and family planning.

Surgical Treatment of Tuberculosis.—Padhi and Lynn (*Indian Journal of Tuberculosis*, vol. 6, December, 1958) reported that such procedures as phrenic paralysis, pneumothorax, and pneumoperitoneum have fallen into disuse in the treatment of pulmonary tuberculosis, their place now being taken by resection. Not a single pneumothorax or pneumoperitoneum was induced in their hospital in the last three years. In the authors' series of 150 pulmonary resections the indications were absolute in 118 and relative in 32; 41 had residual cavities, 38 had residual caseonodular lesions, 36 had destroyed lobes, 24 had destroyed lungs, 8 had tuberculoma or inspissated cavities, and 3 had bronchopleural fistula. Of those with residual caseonodular lesions 32 were subjected to resection as a prophylactic measure against reactivation, as they lived far away from the sanatorium and were likely to be lost to follow-up examinations over long periods. Advanced age was not considered a contraindication if the cardiorespiratory reserve was satisfactory. Thus, 15 patients in this series were 50 to 59 years of age and two were over 60; 16 had extremely poor pulmonary function. They were persistently positive, drug-resistant, and had undergone prolonged sanatorium treatment. The morbidity and mortality in these resections was high, but the risk of operation was preferable to a long downhill course. Of these 16 patients 3 died, but 13 were rehabilitated. Most

of the 150 patients were between 20 and 30 years of age. All had had initial sanatorium treatment with chemotherapy which varied from three months to several years. On admission 139 had positive sputum; 46 had positive sputum and were drug-resistant at the time of resection. Bronchoscopy was performed routinely prior to operation to exclude endobronchial disease; bronchography was done in most of these cases. Deep breathing exercises and diaphragm control were started one week before operation and continued postoperatively.

SWEDEN

Treatment of Psychiatric Patients with Iproniazid.—Norring and Gottfries (*Svenska Läkartidningen*, Jan. 9, 1959) treated 100 patients at the psychiatric department of a general hospital in Malmö with iproniazid. The main indications for this treatment were depressive and asthenic states and the initial dosage was 25 mg. three times a day for a week, after which it was sometimes cautiously raised. The maximum reached was 150 mg. daily. The duration of treatment was up to seven months. In many patients the results were surprisingly good, but there were also many undesirable side-effects leading to withdrawal of the drug within a fortnight in 6 patients and after a longer interval in 17. In 58 patients hypotonic disturbances manifested themselves in giddiness, faintness, tinnitus, and "blackness of vision." Those with already existing hypotonia were much embarrassed by these hypotonic disturbances. Other side-effects were profuse sweating, headache, edema, and stranguria which in two of eight patients required catheterization that had to be continued two days after the drug had been withdrawn. There were also mental disturbances such as hypomania, which was observed in five patients.

Many of the 100 patients had been refractory to other methods of treatment such as electroshock, insulin, and sedatives, so the numerous successes achieved by iproniazid were the more impressive and an incentive to further trial under the closest control of the blood pressure, urine, and body weight. Hypertonic patients and others with a history of liver or kidney disease needed specially close watching. Epilepsy should be regarded as a contraindication for this treatment. The drug gave disappointing results in patients with presenile depressive states.

Cholesterol Metabolism.—Dr. H. Malmros of the University Hospital at Lund (*Nordisk medicin*, Jan. 2, 1959) reported on experiments carried out at his hospital by Dr. G. Wigand who fed rabbits a semisynthetic diet of pellets containing sugar, starch, casein, vitamins, 8% coconut fat, and salts, but no cholesterol. In spite of the total lack of cholesterol in this diet, the rabbits developed marked hypercholesteremia after a few weeks. On the completion of these tests after 110 days, atheromatous changes were plainly demonstrable in the aorta. On the other hand, rabbits fed on corn oil presented normal blood vessels. A series of 30 patients suffering from essential, familial hypercholesteremia were treated during the past two or three years by Malmros as follows: Animal fats in the form of butter, cream, milk, cheese, eggs, and meat fats and such other fats as margarine and cocoa fat were excluded from the diet, and dried milk and cheese from which milk fats had been abstracted and corn oil were substituted. This oil was used for salad dressing, mixed with porridge and mashed potatoes, and used for frying. Vegetables, fruit, sugar, and cereals were permitted, but bread made of wheat and cakes made with butter were omitted. Later fish, even fat fish, was added. Most of the 30 have been on this diet for over a year and they have on the whole tolerated it well. This diet was regularly followed in a couple of weeks by a fall in the serum cholesterol level. In some subjects there was a further fall, and in others the cholesterol maintained a steady level. Further investigations should show whether it is possible by using an appropriate diet to control arteriosclerosis.

When to Prevent Tetanus.—*Svenska Läkartidningen* for Jan. 16 again published (without giving the names of the offenders) cases brought to the attention of the Swedish Doctors' Disciplinary Committee. This time the hardy perennial question was raised: When should a wound be treated to prevent tetanus? A man, aged 63, injured his left index finger in a carding machine on Nov. 10, 1956. The terminal phalanx was amputated at a surgical polyclinic where bruised tissues were removed and the wound dressed. No prophylactic injection of tetanus serum was given but he was given penicillin at that time and again on his return to the clinic on Nov. 12 and 14. On Nov. 21 he returned complaining of severe pain in the finger and some necrotic tissue was removed. On the next day he complained of pain and stiffness in the nape of his neck and jaws. Tetanus being suspected, he was admitted to hospital whence he was discharged on Dec. 10 after having undergone a relatively mild attack of tetanus. While refusing to censure the doctors concerned, the committee took the occasion to quote the opinion voiced by the Swedish Surgical Society in 1951 to the effect that antitetanic serum should not be given merely for safety's sake but solely for real indications. The fact remains that 30 or more cases of tetanus continue to occur every year in Sweden, and the committee quoted the opinion of one of its experts that it would be well for the nation as a whole to be given the triple vaccine (whooping cough, diphtheria, and tetanus) soon after birth.

CORRESPONDENCE

PHYSICAL FITNESS OF YOUTH

To the Editor:—The paper by Lane on "The Role of the Pediatrician in Physical Fitness of Youth" in THE JOURNAL (**169:**421-427 [Jan. 31] 1959) should not remain unchallenged. The American Medical Association has repeatedly called the attention of its members to the fallacy of accepting the norms for physical fitness on the basis of pure muscle strength. It is the well-recognized duty of every physician who treats children to strive for maximum achievement in all spheres of the young patient's development, and the pediatrician today is making a conscientious effort to guide parents toward that goal. He is appreciative of the fact that not all people are born to be athletes or weight lifters. The pediatrician takes more pride in a cardiac child, who as a youth can consider himself physically fit to be gainfully employed, than in a youngster who achieves stature as the captain of a football team.

"As we look about us today," the author states, "mindful of how seriously we took our responsibilities, many of us find cause for more amazement than pride in some of the children we remember as our healthy infant patients. Too often we see deterioration instead of development; young bodies, once firm and flexible, beginning to go slack and soft. We hear about too many backaches and we are appalled." What does the author mean by deterioration? If the implication is "slack and soft," how tight and hard should a muscle be before it is judged physically fit—and fit for what? Also, I am not aware of the great prevalence of backache as a disease of youth, and I have found quite a number of pediatricians who share this opinion. Not a single one seemed appalled by its incidence.

Is a youth to be considered physically unfit if he is too light for a football club or too short for a basketball team? It is the rehabilitationists who have taught us most about the importance of muscle function rather than mass as a criterion for fitness. One of the best pediatric residents we have had recently was a paralytic. He jumped around on crutches, always ready to learn and to serve. The patients loved him, so did the staff. I considered him physically fit, as did everyone who knew him.

At its annual meeting in 1957 the Joint Committee on Health Problems in Education of the National Education Association and the American Medical Association passed a resolution, part of which follows: "The Joint Committee . . . wishes to reiterate its belief that fitness is not a narrow or limited concept relating, for example, only to physical development, nor is it testable only by muscular strength, agility, or flexibility tests. On the contrary, fitness can be judged only through the use of a battery of evaluative procedures including appraisal of all aspects of organic, psychological, and social growth."

HERMAN M. JAHR, M.D.
111 S. 39th St.
Omaha.

RADIATION THERAPY AND LEUKEMIA

To the Editor:—The diagnostic problem in THE JOURNAL (**169:**136-142 [Jan. 10] 1959) is an excellent presentation, and the conclusion reached by the authors seems reasonable and correct. The data from which these conclusions are reached, however, are inadequate—particularly the statement that the development of leukemia was the result of radiation therapy, which in one place was said to be intensive and in another place was simply mentioned as having been given. If radiation therapy is to blame for the development of this leukemia, it would seem logical that data be presented concerning the amounts of radiation given, areas treated, duration of time during which these treatments were administered, physical factors of the equipment used, and other necessary information so that one might arrive at a valid conclusion that excessive radiation therapy did lead to the end-result. Such loose reporting as appears in this article has been common in the literature in the past few years and has done more to harm the practice of radiology than has any other factor in the past few decades.

EUGENE G. TAINTER, M.D.
2909 J St.
Sacramento 16, Calif.

The above comment was referred to the authors of the diagnostic problem, and they have submitted the following reply.

To the Editor:—In view of Dr. Tainter's perfectly justified criticism we would like to submit the following addendum to the diagnostic problem "Erythremia (Polycythemia Vera), Radiation Therapy, and Leukemia."

The x-ray therapy given the patient, at another institution, is detailed as follows: From Sept. 9 to Oct. 10, 1952, a field 100 centimeters square was used to treat the spleen. A total of 750 r (air) was given in nine divided doses, eight from an anterior port and one from a posterior port. From Oct. 23 to

Nov. 6, 1952, an anterior port was used to treat the tibia and fibula, bilateral, entire length, giving 50 r (air) six times, making a total of 300 r (air). An anterior port was used to treat the femora, bilateral, entire length, giving 50 r (air) six times, making a total of 300 r (air). An anterior port was used to treat the upper extremities, giving 50 r (air) six times, making a total of 300 r (air). Factors in treatment of the spleen and extremities are 200 kv., 50-cm. distance from skin to focus, and half value layer of 0.95 mm. of copper. Triethylene melamine therapy was given from May 29, 1953, to Dec. 20, 1956, intermittently in small doses in courses varying from 1 to 13 weeks, in a total dosage of 260 mg.

Daniel S. Kushner, M.D.
629 S. Wood St.
Chicago 12.

FREEDOM FOR THE PROFESSION

To the Editor:—William S. McCann states in his letter to the editor in The Journal (**169:**410 [Jan. 24] 1959) that the changes in the treatment of physicians in the German democratic republic are due to "the strength of a strong professional organization." The fact is that no professional organization of any kind exists here and the changes mentioned in the letter were effected after a study by the central committee of the United Socialistic Party (S. E. D.).

Dr. Ernst Amann
Ernst Thaelmannstrasse 11
Dresden A 1
Germany.

IATROGENIC

To the Editor:—The word iatrogenic was coined several years ago to denote any disease induced by medical treatment. The classic example is cardiac neurosis in a patient whose doctor is too fussy. As such, iatrogenic is probably a useful word, but it is beginning to suffer from misapplication. A good example is the title "Iatrogenic Stiff Shoulders," appearing in the Feb. 28 issue of The Journal, page 945. These stiff shoulders are not produced by the physician, they are produced by the injury and the lack of exercise afterward. To call such a shoulder iatrogenic is akin to calling an embolic death iatrogenic because the doctor did not tie the femoral vein! There might be other factors, too. I think that we should bury the word iatrogenic.

Clifford L. Graves, M.D.
846 Prospect St.
La Jolla, Calif.

MISCELLANY

A BACKGROUND PAPER ON KREBIOZEN

American Cancer Society

Page
I. The Controversy over Krebiozen....1790
II. What Is Krebiozen?....1791
III. The Men Behind Krebiozen....1791
IV. Organizations Connected with Krebiozen....1792
V. Has Krebiozen Ever Been Tested?....1792
VI. Can Krebiozen Be Tested?....1794
VII. Is Krebiozen Patented? Can It Be Sold?....1795
VIII. Publicity and Promotion of Krebiozen....1795
IX. National Cancer Institute Requirements....1796
X. The American Cancer Society and Unproved Drugs....1797
XI. Conclusions....1797

I. The Controversy Over Krebiozen

During the past seven years the owners and proponents of Krebiozen, a substance alleged to be beneficial in the treatment of cancer, have been engaged in a great campaign to publicize this substance. They have been disseminating propaganda through articles strategically placed in newspapers, magazines, and books, as well as by organized letter writing, and they have been using national political channels to further their interests. They have already been involved in legislative investigations in two states, California and Illinois.

According to Herbert Bailey's book, "A Matter of Life or Death" (New York, G. P. Putnam's Sons, 1958), these individuals have made it clear that they wish to recoup from the sale of the substance an investment claimed to be about 2 million dollars and that they intend to sell the substance for profit as a proprietary drug. Despite this fact they have repeatedly petitioned health organizations supported by public funds to underwrite a test of the therapeutic efficacy of Krebiozen in collaboration with them. They have hoped to use public funds to defray the cost, estimated at $500,000 or more, of testing this privately owned substance.

Moreover, the chemical composition of Krebiozen remains unknown. The recent claims of its therapeutic efficacy which they have broadcast are based on case histories of patients treated with Krebiozen, although they have not given independent investigators access to these records within the last five years. The owners and proponents have demanded that the substance be tested according to their own terms, which are demonstrably unscientific.

Their steady campaign of publicity ostensibly designed to obtain support from either the American Cancer Society or the National Cancer Institute for testing the substance on their own terms has

News release of the American Cancer Society dated March 9, 1959.

aroused public interest in Krebiozen. The following documentation which chronicles the history of Krebiozen will provide answers to some of the questions which the public has been asking about this unproved substance.

II. What Is Krebiozen?

Krebiozen is a coined name applied to an alleged anticancer drug. It is said to have been produced by Dr. Stevan Durovic in Argentina prior to 1949. Dr. Durovic claims that he injected 2,000 Argentinian horses with Actinomyces bovis, a microorganism which causes "lumpy jaw" in cattle, and from the blood of these infected horses he extracted 2 Gm.—about one-half teaspoonful—of a whitish powder which he named Krebiozen. The full details of the method of extraction have never been revealed. Later, Dr. Durovic brought this powder to the United States. Here, without prior chemical analysis of the powder, he dissolved it in no. 9 mineral oil in the ratio of one part of Krebiozen to 100,000 parts of mineral oil. Thus he made the original (and only) supply of Krebiozen amounting to 200,000 doses, 1 cc. each.

III. The Men Behind Krebiozen

Dr. Stevan Durovic°.—Born in Ulcinj, Yugoslavia, in 1905, Dr. Durovic received the degree of Doctor of Medicine from the University of Belgrade in 1930. He did postgraduate work at the University of Vienna and at the Pasteur Institute in Paris. During World War II, as a captain in the Medical Corps of the Royal Yugoslav Army, he was taken prisoner by the Italian army and was held for 18 months. In 1942, on the basis of his being a physician in ill health, he was released and he traveled to Spain and Argentina on a Yugoslav passport with a Vatican visa. In 1944 in Buenos Aires, he established Duga, S. A., which was financed by his brother Marko Durovic, a former munitions manufacturer. At the Duga laboratories he prepared a "whitish powder" which he named Kositerin and which he thought was useful for treating high blood pressure. Dr. Durovic visited the United States in March, 1949, for the purpose of working with doctors at Northwestern University in testing Kositerin. Kositerin was found to be without value for the treatment of high blood pressure.

In August, 1949, Dr. Durovic met Dr. Andrew C. Ivy, a distinguished medical researcher and vice-president of the University of Illinois. At this time Dr. Durovic told Dr. Ivy about another substance, Krebiozen, which he believed was effective against cancer, and he solicited Dr. Ivy's help in testing the drug.

°Details of Stevan Durovic's career before he came to the United States are based on a pamphlet published in June, 1953, by the Krebiozen Research Foundation, and on a letter, now in the files of the National Cancer Institute, from the foundation's secretary.

Dr. Durovic is not licensed to practice medicine in this country. He has stated that he is interested only in research, but he has not published in any scientific or medical journal in this country during his nearly 10 years of residence here. In July, 1952, he was granted permanent residence in the United States through Senate Bill 1159, sponsored by Senator Paul Douglas of Illinois. In September, 1958, he became a naturalized citizen of the United States.

Dr. Andrew C. Ivy.—Born in Farmington, Mo., in 1893, Dr. Ivy received his Ph.D. from the University of Chicago and his M.D. from Rush Medical College. He has been the author or co-author of many published scientific articles. Numerous honorary degrees have been awarded to him, and he has held important posts in several universities, in the government, and in private organizations. He was at one time scientific director of the Naval Medical Research Institute, executive director of the National Advisory Cancer Council, and consultant (on war crimes) to the Secretary of War. When he met Dr. Durovic in 1949, he was vice-president-in-charge of the Chicago Professional Colleges of the University of Illinois and distinguished professor of physiology and head of the department of clinical science at the university.

Although he had not previously published any papers on Krebiozen in medical journals, at a meeting in the Drake Hotel in Chicago on March 26, 1951, attended by physicians and laymen including members of the press, Dr. Ivy submitted a privately printed, 106-page brochure which favored Krebiozen and of which he was co-author. The meeting was widely publicized in newspapers and there was a public furor over Krebiozen. Because of the methods Dr. Ivy had used to promote Krebiozen, his membership in the Chicago Medical Society was suspended for three months. Although he was later invited to reinstate his membership, he declined to do so and was dropped from the roster of the society for nonpayment of dues. This action automatically terminated his membership in the Illinois Medical Society and the American Medical Association.

Dr. Ivy has stated that the process of manufacturing Krebiozen has not been revealed to him and that he has neither seen nor analyzed the original substance in the undissolved state. He has also stated that in Chicago he has extracted a substance from 40 horses, recreating by deduction the process that Dr. Durovic used to extract Krebiozen in Argentina. Dr. Ivy is reported to have obtained 10 times the amount of powder that Dr. Durovic claimed to get from the same number of animals. However, since the composition of Dr. Durovic's powder has never been revealed, there is no way of knowing whether the substance extracted by Dr. Ivy in the United States in 1957 is the same as that obtained by Dr. Durovic in Argentina eight years before.

Several other physicians in association with Dr. Ivy have privately published monographs on Krebiozen. These men are Dr. J. F. Pick, a plastic surgeon; Dr. W. F. Phillips, a general practitioner; and Dr. L. Krasno, a researcher in antibiotic dusts.

Marko Durovic°.—Born in Ulcinj, Yugoslavia, in 1900, Marko Durovic, brother of Stevan Durovic, received his legal training at the University of Paris and the University of Belgrade, completing his training in 1923. In 1926 he was appointed judge in the Yugoslav District Court in Belgrade. He practiced law from 1927 to 1941 and was co-owner of Vistad, a munitions plant. In 1942 he was seized by Italian troops and was sent to Rome. Through the intercession of the Vatican he was released and allowed to travel to neutral Argentina with his brother. There he bought a steel plant and the Instituto Biologica Duga and underwrote his brother's experiments which produced "Kositerin." He came to the United States in 1950 on a visitor's visa. In July, 1952, he was granted permanent residence in the United States through Senate Bill 1159, sponsored by Senator Paul Douglas of Illinois. In September, 1958, he became a naturalized U. S. citizen.

IV. Organizations Connected with Krebiozen

A number of organizations have been created by the supporters of Krebiozen to publicize, promote, and distribute the drug and/or to obtain public support for the testing of Krebiozen according to the terms laid down by its proponents. These organizations are:

1. Duga Laboratories, Inc., Chicago, and Buenos Aires, Argentina. This drug firm was established by Marko Durovic to underwrite Dr. Stevan Durovic's experiments which produced Krebiozen. Duga Laboratories, Inc., distributes Krebiozen to physicians through the Krebiozen Research Foundation (see below), which it supports. Duga Laboratories, Inc., accepts from the foundation moneys which the foundation receives as contributions from patients who have been given Krebiozen. According to Herbert Bailey's "A Matter of Life or Death," Dr. Durovic has stated that the Duga Laboratories, Inc., is in debt to creditors who expect to receive a return on their investments if Krebiozen is proved to be an effective cancer remedy.

2. The Krebiozen Research Foundation, Chicago. This foundation is registered in the state of Illinois as a nonprofit corporation. It furnishes Krebiozen to selected physicians for use in treating patients. The necessary steps under the Public Health Service Act have never been taken to make it possible for Krebiozen to be sold for use in interstate commerce (see section VII). However, the recipient is requested to make contributions to the Duga Laboratories, which supports the foundation. The request for contributions is at the rate of $9.50 per ampul. The Foundation Library Center reports that as of February, 1959, the Krebiozen Research Foundation had not published a list of officers, a report of activities, or a financial statement.

3. Committee for Independent Cancer Research, Inc. Originally formed ostensibly to investigate various cancer remedies, this organization has put forth major efforts to promote Krebiozen and a book "Krebiozen, Key to Cancer?" written by Herbert Bailey, president of the committee. Because of a disagreement over a matter of policy, this committee has since split into two divergent groups: (*a*) The Freedom for Cancer Research Committee. Mr. David M. Kasson, who claimed he had been treated for cancer with Krebiozen, presided over this committee. Upon his death from cancer in June, 1958, the committee was dissolved. (*b*) The Independent Cancer Research Foundation, Inc. Miss Gloria Swanson, former chairman of the Committee for Independent Cancer Research, serves as a member of the board of directors. This group is devoted to gathering and disseminating "all possible information on trends in cancer research and treatments."

4. Committee for a Fair Test of Krebiozen, Inc. This group has circulated petitions urging the American Cancer Society to support the method of testing of Krebiozen which its proponents are demanding.

5. The Lakeland Foundation of Chicago. This organization has also been involved in the Krebiozen controversy. According to the Foundation Library Center it is a private corporation and is incorporated under a broad charter that includes conservation of natural resources, care of the aged, research in economic science, and medical research in the field of malignancy. The Lakeland Foundation does not currently publish an annual report.

The Lakeland Foundation has come to Dr. Ivy's assistance on two occasions. When he was on a leave of absence from Jan. 1 through June 30, 1953, from the University of Illinois and without salary, the foundation loaned him $5,000 for living expenses. In 1956-1957, the Lakeland Foundation advanced the sum of $10,000 to Dr. Ivy for the purpose of recreating Krebiozen.

V. Has Krebiozen Ever Been Tested?

1. (*a*) The powder form of Krebiozen was never chemically analyzed before being dissolved in mineral oil. An analysis of Krebiozen dissolved in no. 9 mineral oil has been done by the Clark Microanalytical Laboratory, Urbana, Ill., and was reported in *Chemical Week*, June 16, 1956. According to the Clark analysis, "It contained no nitrogen and . . . might contain some sulphur in addition to carbon, hydrogen and oxygen. Infra-red and ultraviolet

°Details of Marko Durovic's career before he came to the United States are based on a pamphlet published in June, 1953, by the Krebiozen Research Foundation, and on a letter, now in the files of the National Cancer Institute, from the foundation's secretary.

spectroscopy revealed absorption bands indicating that it could be either a polysaccharide or a steroid. A further study of the product is required before a more definitive statement about its chemical structure can be made."

(*b*) Two distinguished chemists, Drs. Paul Kirk of the University of California and Arthur Furst of Stanford University, testified at the 1958 hearings of the California General Assembly Committee on Public Health that they had independently attempted to extract and to analyze Krebiozen. After the most exhaustive tests Dr. Kirk independently concluded that "the extraction failed to reveal the presence of anything dissolved in the ampules and would lead to the supposition that all that is contained in Krebiozen is mineral oil, Nujol, to be specific, because the analysis indicated the identity with Nujol." Dr. Furst concurred. "I say it is pure Nujol," he stated.

Dr. Ivy has challenged this testimony.

2. (*a*) A few animal studies have been done with Krebiozen by its proponents. From these studies it is claimed that the substance is nontoxic in rats, cats, and dogs.

(*b*) Twelve dogs were said to have been treated with Krebiozen by Dr. Hannibal DeGrana at the School of Veterinary Medicine of the University of Buenos Aires. All the animals were described as having natural cancer; seven animals were said to be almost blind because of cataracts. It was said that all of the tumors were affected to some degree and that in six dogs the cataracts cleared and the dogs regained sight.

(*c*) John B. Loefer, Ph.D., of the Southwest Foundation for Research and Education, San Antonio, Texas, reported on the effects of Krebiozen therapy on transplanted mouse leukemia and lymphosarcoma in THE JOURNAL of the American Medical Association on May 17, 1952. "Krebiozen . . . did not affect the course of development of either the leukemia or the lymphosarcoma," he wrote.

3. (*a*) In 1952, the Committee on Research of the Council of Pharmacy and Chemistry of the American Medical Association published "A Status Report on Krebiozen" in THE JOURNAL of the American Medical Association. This report, made by a group of four distinguished educators from several medical schools in Chicago (excluding the University of Illinois), contained an analysis of 100 case histories of patients treated with Krebiozen. The case records had been received from seven sources and were examined at the request of Dr. Ivy and his associates at the Krebiozen Research Foundation.

"Ordinarily, the Committee on Research . . . would not attempt to evaluate the clinical benefits, if any, of a substance whose character and method of manufacture were not known and standardization of which was so loosely defined," the A. M. A. report stated. "However . . . tremendous worldwide public interest created a moral obligation . . . which transcended the issue of medical ethics ordinarily applicable to secret remedies."

The conclusions of this report were:

"Ninety-eight (of 100 cases studied) were reported as failing to show evidence of improvement.

"Two patients showed some evidence of temporary improvement coincident with Krebiozen therapy. In one patient this was apparently fortuitous; in the other major lesions showed continued rapid progression."

(*b*) Seven investigators reported on 63 cancer cases treated with Krebiozen to the Committee on Cancer Diagnosis and Therapy of the National Research Council. The committee then reviewed these and other cases in 1951 and found "no evidence of any curative effect and no proof of palliative effect attributable to the 'drug' itself." This opinion was based on an analysis of the 100 cases already reported in THE JOURNAL, some of which were included among the 63 cases studied by the Committee and the 22 cases reported by Dr. Ivy and others in the booklet distributed at the meeting in the Drake Hotel on March 26, 1951, when Krebiozen was first announced.

(*c*) In 1952, a committee of six distinguished physicians from several medical schools, headed by Dr. Warren H. Cole, head of the department of surgery of the University of Illinois, was appointed by Dr. George Stoddard, president of the university, for the purpose of reviewing Dr. Ivy's 500 cases of cancer treated with Krebiozen. The committee's report, presented to the trustees of the university, contained the following significant conclusions: "Ignorance of the material interferes with a sound evaluation of its therapeutic effectiveness . . . no acceptable evidence that any malignant tumor had been cured by Krebiozen . . . no evidence of prolongation of life . . . no histological evidence that Krebiozen produced degenerative or regressive changes in tumor cells . . . no radiographic evidence that Krebiozen could reduce metastatic tumor lesions in bones or lungs . . . statement in Dr. Ivy's report that a large majority of patients reported a decrease in pain was not confirmed."

In a discussion of future tests, the Cole committee advised that a supply of Krebiozen should be made available for testing and that investigators should attempt to reproduce the material and determine its chemical content.

(*e*) A committee of supervision, under the chairmanship of Dr. Robert E. Johnson, head of the department of physiology, Urbana, Ill., was appointed by Dr. Stoddard to carry out the recommendations of the Cole committee. The committee of supervision reported in part that "a supply of the original material was needed so that it could be tested directly. A supply of the vehicle was needed for adequate scientific control. Complete information on the mode or modes of preparation was needed

. . . the originators of the preparation are unwilling to furnish materials and will not provide full technical information . . . (therefore) the committee is unable to proceed further."

(*f*) In 1952, after a 21-month investigation, Dr. Stanley P. Reimann, director of the Institute for Cancer Research, Philadelphia, announced: "We now know we have cured no patients [with Krebiozen] and we don't believe the length of life has been prolonged on any we have treated."

4. The proponents of Krebiozen have been involved in legislative investigations in two states and have received support from at least two U. S. Senators and one U. S. Representative.

(*a*) The Illinois legislature: In 1953, a joint committee of 14 Illinois legislators was appointed from the two state legislative bodies to investigate the Krebiozen controversy. In 1954, after extensive hearings for which records were subpoenaed, this committee concluded that Dr. Ivy and the Durovic brothers "were men of good character" and that neither Dr. Stoddard nor the American Medical Association had conspired against Dr. Ivy. The committee urged further research on Krebiozen but made no recommendations as to how this research was to be conducted.

(*b*) The California Senate: In 1958, the California Senate Committee on Public Health held hearings on "Fraudulent, Dangerous, Unscientific and Deceptive Practices in the Field and Treatment of Disease" at which Dr. Ivy testified. The burden of Dr. Ivy's testimony was directed to the advocacy of a "double-blind" test of Krebiozen which its proponents have been endeavoring to get.

(*c*) The late Senator Charles W. Tobey: Senator Tobey is reported to have sponsored an investigation of Krebiozen by a staff investigator.

(*d*) The Honorable Roland V. Libonati, U. S. Representative from the State of Illinois: On several occasions, Congressman Libonati has had remarks on Krebiozen inserted in the Congressional Record. His remarks have generally echoed Dr. Ivy's.

(*e*) Senator Paul Douglas of Illinois: Senator Douglas sponsored a bill in the U. S. Senate which gave the Durovics permanent residence in the United States. On the floor of the United States Senate, in August, 1958, Senator Douglas proposed a "Fair Test of Krebiozen" to be done by the National Institutes of Health, a U. S. Government institution. Later, Drs. Ivy and Durovic met with Dr. Heller, director of the National Cancer Institute of the National Institutes of Health, and with a representative of Senator Douglas. At this meeting, Dr. Heller stated that "the first step should be an examination of the case records in possession of the Krebiozen Foundation."

At a meeting on Sept. 24, 1958, attended by Drs. Ivy and Durovic, Senator Douglas's representative, and Dr. Heller, it was generally agreed that the evaluation of Krebiozen should be explored further and that the group was seeking to develop an agreed procedure that would be acceptable to the scientific community.

On Dec. 5 at another meeting attended by the same group, this time including Senator Douglas, the National Cancer Institute suggested an examination of Dr. Ivy's data by a committee of mutually acceptable scientists to decide whether clinical trials should be undertaken and how they should be undertaken. Senator Douglas expressed the opinion that this suggestion was a proper one. Dr. Ivy was invited to define his role as consultant to the evaluating committee, to which he had agreed.

He answered in a letter to the Institute dated Feb. 1, 1959, insisting that he personally should be a member of "an arbitration type of committee" and "a party to the administration of the therapy and the interpretation of the results under conditions where bias cannot operate." This is a procedure which, as pointed out in two conferences attended by Dr. Ivy, could admit bias and would not be acceptable to the scientific community.

The Institute responded to Dr. Ivy's letter on Feb. 6 by asking him to clarify his apparent rejection of the previous plan made between him and the National Cancer Institute, because "it is the desire of the Institute to get on with the evaluation of Krebiozen as soon as a scientifically acceptable procedure can be effectuated."

VI. Can Krebiozen Be Tested?

The proponents of Krebiozen have frequently stated that they would welcome an evaluation of their preparation, and during the last two years they have conducted an active campaign to promote a specific type of evaluation which they have outlined as a "double-blind" test.

In the past, an evaluation of Krebiozen by independent researchers has been obstructed because of lack of information about the substance and its preparation and the unavailability of the substance. Thus, the Committee on Supervision, which was appointed at the University of Illinois in 1952, was unable to proceed with an evaluation of Krebiozen.

Also, independent evaluation of Krebiozen has been impeded because of inadequate information about the drug, the unwillingness of its proponents to surrender to independent researchers the case histories on which they base their claims, and the insistence of the proponents that Krebiozen be tested only on the terms which they themselves have set forth—terms which have been unacceptable to reputable scientists unassociated with Krebiozen.

Recently, the supporters of Krebiozen have concentrated their propaganda efforts on trying to get a reputable organization to sponsor a "double-blind" study of their substance.

The proposal for such a study was first made to the American Cancer Society in 1958 by James L. Griffin, Director of the Krebiozen Research Foundation.

Briefly, the study proposed by Mr. Griffin called for the appointment of a committee of laymen and a committee of physicians, one-half of the members of each committee to be selected by the Krebiozen proponents and one-half to be chosen by the American Cancer Society. Each committee would then select a single additional member. Ampuls of plain mineral oil and ampuls of Krebiozen identified only by code numbers would be administered by Dr. Ivy to known cancer patients. The extra member of the lay committee would be the only person to know the identity of the contents of the ampuls, and he would be instructed to keep the code list in a safety deposit box.

At the end of the period of treatment Dr. Ivy would evaluate the results and undertake to identify the patients who had received Krebiozen and those who had not. Committee members would be permitted to observe the patients and to take notes during the treatment period.

The Krebiozen proponents claim to have 1,200 case records of patients already treated with Krebiozen. In testing an unproved substance, the first step would be to evaluate the results already achieved, and in this case it would mean an analysis of the alleged case records. In its proposal to the American Cancer Society, the Krebiozen Research Foundation, however, refused to permit an examination of these case records, unless the Society agreed beforehand to sponsor their suggested study.

Their proposal for this particular study was carefully considered by the American Cancer Society's Advisory Committees on Research and on the Therapy of Cancer and by the Society's Research Advisory Council. These three groups of scientists concluded that this proposal "does not provide a scientifically valid plan for conducting an objective and meaningful evaluation." Their opinion was adopted by the Board of Directors of the American Cancer Society on Oct. 24, 1958.

The first reason for rejecting the proposal was that the committees to be set up as outlined by the Krebiozen proponents would not be truly independent research groups, because one-half of the membership of each committee would consist of individuals selected by the proponents.

The second reason was that the plan stipulated that only Dr. Ivy would administer the Krebiozen. The American Cancer Society felt that this would not permit "an opportunity to determine whether physicians generally can obtain the same results."

The third reason for rejecting the proposal was that the plan "provides no clear-cut standards for either measuring the result desired or defining or measuring the results obtained."

The Society further stated that it would be willing to support "the testing of any substance proposed for the prevention, treatment, or cure of cancer, provided the substance is available for testing under the well-established scientific methods known and accepted for all products proposed for human use, and further, provided that satisfactory preliminary evidence exists that the substance has shown promise of being useful in the treatment of cancer."

The American Cancer Society itself cannot test any drug. It does not operate research laboratories, nor does it control hospitals or other facilities for the treatment of cancer patients. The Society has clearly made it a matter of record that it favors the full knowledge and testing of Krebiozen.

VII. Is Krebiozen Patented? Can It Be Sold?

The owners of Krebiozen have stated on numerous occasions that they have a large investment in this substance and intend to market it for profit. For this reason they are concealing the details of the manufacturing process, thereby setting up a barrier to the testing of the substance by independent researchers.

If the owners of Krebiozen wish to protect the substance, they may apply for a patent on it. They may also apply for a patent on the process by which it is made. Hundreds of drugs are manufactured in this country under such patents.

Such applications are temporary protection for the proponents while the patents are being searched.

Some years ago the owners of Krebiozen applied for a patent but when the U. S. Patent Office returned the application with request for further information, the owners of Krebiozen failed to supply this information and did not resubmit their application. Hence, there is no patent or new application for a patent on Krebiozen, either the substance or the process, in the files of the U. S. Patent Office as of January, 1959.

By its description Krebiozen is subject to the biological control provisions of the Public Health Service Act and thus it may not be legally shipped for sale, barter, or exchange in interstate commerce or exported from or imported into the United States, unless it is produced under government license. No application for such license has ever been completed for Krebiozen. If an application were made, supported by adequate evidence of safety, purity, and potency of the product, it would be the responsibility of the Division of Biologic Standards of the National Institutes of Health to recommend whether or not a license should be issued. Without this license Krebiozen may be distributed only to qualified experts, solely for purposes of clinical investigation, but it cannot be sold. Some physicians, as indicated in section IV, have obtained Krebiozen in this way since 1952.

VIII. Publicity and Promotion of Krebiozen

The history of Krebiozen has presented elements both of wide publicity and of deep secrecy. Some of the proponents, although they are physicians and well acquainted with the accepted procedures for

introducing a new substance, have ignored and flouted these procedures in the case of Krebiozen. From the very first they have sought to arouse the public interest in Krebiozen before adequately demonstrating to the medical profession the utility or efficacy of the substance.

For this unorthodox approach, Dr. Ivy was disciplined by the medical society of which he was a member. He consequently was relieved of his position as vice-president of the University of Illinois. Such censure, however, has not deterred him from continuing to publicize Krebiozen. He has since appeared on television and radio programs devoted to the promotion of the drug, has held interviews with the press, and has made other public appearances in behalf of Krebiozen.

An example of Dr. Ivy's methods of attracting publicity is provided by the circumstances of his recent letter to Dr. Harold S. Diehl, senior vice-president for research and medical affairs of the American Cancer Society, proposing a test of Krebiozen. Dr. Ivy was not content merely to communicate privately with Dr. Diehl. At the time he sent this letter, he also released copies of it to the press in an obvious effort to create publicity.

The press releases that have been issued by the proponents of Krebiozen, or in their behalf, are not always consistent with the facts. For instance, G. P. Putnam's Sons, publishers of the new book "A Matter of Life or Death, the Incredible Story of Krebiozen" by Herbert Bailey, issued a press release stating that "'the evaluation of Krebiozen—the controversial anticancer agent—by the National Cancer Institute is under way and will proceed with all possible speed,' Dr. John R. Heller, the Institute's Director told Herbert Bailey (sic)." This release, dated Nov. 11, 1958, also declared that the National Cancer Institute had agreed to conduct a "double-blind" test of Krebiozen. Herbert Bailey, who apparently prepared the Putnam release, had sent a copy of it, prior to its publication, to Dr. Heller for his suggestions. Dr. Heller answered immediately, on Nov. 6, 1958, correcting two inaccuracies in the copy: (1) the evaluation of Krebiozen is not under way, and (2) the method of testing has not yet been agreed upon and cannot be determined until examination of data has been completed. "Actually," wrote Dr. Heller, "we are now approaching the preliminary stage of examining the data submitted by Dr. Ivy to determine whether it warrants further investigation of the treatment."

Although Dr. Heller's comments were sent to Mr. Bailey five days before the press release was published, Mr. Bailey replied that they were received too late for the necessary revisions to be made.

It has also been pointed out by Dr. Heller that on Sept. 24, 1958, when he and other members of the National Cancer Institute met with Drs. Ivy and Durovic to discuss the testing of Krebiozen, Drs. Ivy and Durovic subscribed to a press release issued by the National Cancer Institute which stated that the method of testing Krebiozen should be acceptable to the scientific community. At that meeting, there was no agreement to undertake the "double-blind" study proposed by Dr. Ivy and which had already been widely rejected by scientific investigators.

IX. National Cancer Institute Requirements

The conditions under which the National Cancer Institute would consider an investigation of Krebiozen are based on principles long accepted by the scientific community at large. They apply to the testing of any drug, the value of which has not been adequately proved. These accepted conditions were first outlined by the National Advisory Cancer Council as guide lines for the National Cancer Institute in evaluating compounds and are subscribed to by the American Cancer Society. They are the following:

1. The chemical formula, if known, must be disclosed to the National Cancer Institute, or if not known, the method of preparation must be supplied.

2. Adequate amounts of the chemical having known purity must be available.

3. The evidence upon which any claim of efficacy is based must be presented along with a full explanation of the method of treatment.

4. The National Cancer Institute reserves the right to determine if, how, where, when, and by whom the investigation is to be carried out.

5. The scientists making the investigation will have the right to publish the results.

The National Cancer Institute is willing to undertake an evaluation of claimant's data on an unorthodox treatment claimed to effect cancer cures in humans, provided that the following conditions are accepted:

1. The method of treatment must be fully explained. There must be full disclosure to the National Cancer Institute of the composition or nature of the treatment.

2. Complete records of clinical and laboratory findings must be submitted of the total number of patients with cancer treated with the remedy or method in question. These records must demonstrate the following: (*a*) Diagnosis of cancer in each case, confirmed by verifiable microscopic examination. (*b*) Detailed and documented objective evidence that malignant neoplastic disease has disappeared or that its progress has been arrested for a significant period of time in a significant number of patients. It must be shown that no definitive treatment other than the one in question was used during this period of observation; in addition, a detailed record of all treatment received by the patients prior and subsequent to the test period must be supplied. (*c*) Details as to preparation, dosage, frequency, and route of administration of the agent in question. (*d*) Complete details as to physical and supportive laboratory findings and histological studies in the patients prior to, during,

and subsequent to the course of and cessation of the treatment in question. (*e*) Objective evidence of regressions of primary tumor and metastases as shown by recorded measurements of observable tumors, photographs, and x-rays, with dates of observation.

3. The National Cancer Institute reserves the right to determine whether or not the evidence submitted warrants further investigation of the proposed treatment and its results and reserves the right to determine where, when, by whom, and under what conditions such investigation will be made. The National Cancer Institute reserves the right to make public its findings.

X. The American Cancer Society and Unproved Drugs

Under the American Cancer Society's research program, hundreds of organic and inorganic compounds have been screened and a few substances have been found which are palliative in certain types of human cancer. The results of research on all of them were first published in medical journals. All of these substances can be manufactured by a drug concern and all are readily available to doctors and to hospitals for experimental purposes.

The American Cancer Society is dedicated to the task of finding the cause and the cure of human cancer at the earliest possible moment. To this end, it supports scientific investigation of every promising kind. At the same time, however, it has the responsibility of seeing to it that the public is not misled by enthusiastic claims of individuals who would exploit unproven methods or drugs for the treatment of cancer. Ill-advised reliance on such unproven methods or substances militates against possible cure of the disease by the acceptable methods known at the present.

Any drug which is claimed to cure cancer must fulfill certain objective criteria. Krebiozen has not met these standards. No acceptable evidence that treatment with Krebiozen causes any objective benefit in human cancer has yet been offered by independent researchers.

XI. Conclusions

Advocates of Krebiozen have demanded through all publicity channels what they describe as a "fair test" of the drug. The National Cancer Institute of the United States Public Health Service is willing to conduct a test to further evaluate Krebiozen but insists that it be done in a manner acceptable to the scientific community.

The Krebiozen Research Foundation, Dr. Ivy, Dr. Durovic, and their associates have long claimed they have a tool useful against cancer: it is, then, their clear duty to thousands of cancer patients to cooperate with the National Cancer Institute or any group of competent, objective scientists in an objective test of the drug. Delays now are clearly the responsibility of the Krebiozen Research Foundation.

When Krebiozen was first announced, it was tested in hospitals, clinics, and laboratories, according to scientifically accepted procedures. The results of the tests carried out by scientists and clinicians were reviewed in reports mentioned in section IV. This avenue of testing still remains open to advocates of Krebiozen.

However, the agitation continues. This has an unsettling effect on cancer patients, their families and friends, who question whether the extraordinary claims about Krebiozen are true. The answer can only be settled by a thoroughly objective study such as the one the National Cancer Institute has indicated it is willing to make.

The American Cancer Society hopes that the Krebiozen Research Foundation will recognize the integrity of the National Cancer Institute of the United States Public Health Service and respect its well-established methods and procedures and that the foundation will drop its demands for its own rules and procedures.

THE WORLD'S PLAYGROUND

Known for three generations as the world's playground, Atlantic City has the world's largest compact playground for children, seven miles of beach blocked off by a boardwalk on which no auto traffic is allowed. When physicians gather in Atlantic City, June 7-12, for the convention of the American Medical Association, many will bring their wives and children. The city has merry-go-rounds, Ferris wheels, auto whips, boat rides, caterpillar thrills, airplane rides, tilt-a-whirls, and other breath-taking amusements. Dotting the Boardwalk are Pennylands and Funlands where youngsters can find delights all day for nickels and dimes. They can play miniature baseball and basketball, ride "jet" airplanes and submarines, and hunt miniature moving bears and lions. They can try to ring a prize, test their bowling prowess, or push around golf balls on miniature courses decorated with Disney or Mother Goose characters.

Steel Pier is also a happy place for children. Appealing to adults as well are its famed diving horses, which leap from a 40-ft. platform into a tank with girl riders astride their bare backs, and its water circus with crazy clowns. Steel Pier also has a sea-zoo, a children's theater, a Ripley's Believe-It-or-Not exhibit, and a picnic deck.

In addition to the special programs provided by Atlantic City's hotels and motels, the resort also has in operation during the summer 21 children's playgrounds, as well as shuffleboard courts, bowling alleys, and roller skating rinks, which older children can enjoy. The Boardwalk also has dozens of stores specializing in novelties and toys. In June, when the physicians will be here for the big A. M. A. powwow, manufacturers and distributors will be stocking these stores with new toys.

THE LEISURE CORNER

FLYING PHYSICIANS

Man's desire to achieve flight has been evident from early times. Myths and legends of many peoples relate adventures in flying, one of the most familiar being the Greek myth of Daedalus and Icarus. In the 13th century Roger Bacon proposed the construction of a flying machine with wings that could be operated by the person being carried. The detailed observations, explanations, and drawings found in the notebooks of Leonardo da Vinci mark the beginning of scientific studies of flight. Flight was first successfully accomplished in 1783 in a lighter-than-air device today known as a balloon.

At the beginning of the present century aviation was still in its infancy. Only a handful of men were interested even in gliding. When the Wright brothers made their first flight in a powered, heavier-than-air craft in 1903, they stayed in the air only a few seconds. Today the airplane has created a vast and growing industry, revolutionizing travel and warfare and bringing about tremendous changes in commerce, science, international politics, and the world's standard of living.

Insofar as flying pertains to the practice of medicine, stories about mercy flights to save lives have become commonplace in newspaper accounts. Physicians and nurses have been flown into areas cut off by floods, fires, and other disasters. Sick and injured people have been flown from their homes to hospitals hundreds of miles away in a short time. Moreover, airplanes and helicopters have been equipped as flying ambulances and are used to hunt for and rescue persons lost in forests, at sea, or on mountains. Special drugs, medicines, and isotopes are transported quickly in emergency situations, whereas without the airplane the matter would be time-consuming.

As a hobby for doctors, an excellent way to get off crowded highways and enjoy the wondrous beauties of the wide blue yonder is to own and fly a private airplane. There is much difference between piloting a small private airplane and traveling on a large commercial aircraft. An individual flying on his own must learn the art, get accustomed to the air, and depend on his own skill and judgment. The attributes of skill and judgment should not be alien to a physician, since he is always confronted by situations requiring their application in daily medical practice.

Many persons find they can solo after about eight hours of dual instruction. Experience accumulated during a period of preliminary flight training usually will influence one either to continue with enthusiasm or to drop completely the idea of pursuing further the hobby of flying. One of the most frequent causes for giving up flying a small airplane is the fear of becoming lost, especially during heavy fog. Although the experience of being lost is sometimes terrifying, most flyers regain their confidence quickly.

The student pilot immediately becomes aware that it is not the engine alone but the entire shape and construction of the airplane that cause it to fly. To illustrate, gliders fly without the aid of engines. The beginner must therefore learn something about the nature of air—that it will hold him up just as water holds a swimmer up when he acquires confidence and learns to handle himself properly. Too many people think of a small airplane in terms of an automobile or a motor boat, to be steered around all the curves. The truth is that an airplane is more like a bicycle, which has to be balanced around curves.

You will find that when you pilot your own airplane you will see much more than when you were a passenger on a huge commercial airliner. The need for seeing is important; the pilot needs to see where he is going. In addition, say the owners of private airplanes, the ability to see the surroundings is the very heart of the pleasure to be derived from piloting a private airplane.

Ordinarily, it is not advisable to buy an airplane at the first flush of one's original enthusiasm for flying. The situation is not comparable to buying an automobile in order to learn how to drive it. It is best to learn the art of flying at a reliable flying school. Then, when this is accomplished satisfactorily, the next step is to rent an airplane; under these circumstances, the owner of the airplane will be justifiably concerned for the safety of the pilot. Eventually the pilot will be able to evaluate the characteristics of small airplanes and will be ready to consider purchasing his own.

After a sufficient period of practice in the air the new pilot realizes that he is obtaining an entirely fresh view of the countryside, together with a thrilling, exuberant feeling of well-being and personal satisfaction. Many private pilots take trips to North Dakota. When asked why, they answer: "The landings are unlimited, as far as the eye can see; the fields are big and flat as a table, much larger than airports." When planning a vacation in a private airplane, there arises always the possibility of viewing new vistas and aspects of the United States hitherto unseen and unvisited. Everything the flying physician will want to see is within easy flying distance, no matter what the point of origin. California can be reached from Chicago in easy, relaxed hops; the trip from Chicago to New Orleans requires but one day of solo flight; the trip from Seattle to San Francisco is delightful and takes merely a few hours. Flying in a private airplane can become the most liberating of all hobbies.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Cardiac Catheterization: Risks, Inconveniences, Indications and Contraindications: Study Based on 500 Observations. F. Rovelli. Minerva med. 49:4102-4111 (Nov. 3) 1958 (In Italian) [Turin, Italy].

The author reports on 500 cardiac catheterizations performed for diagnostic purposes on 469 patients, between 4 months and 52 years of age, with congenital or acquired cardiopathy. Of 231 patients with acquired cardiopathy, stenosis of the mitral valve was present in 98, defect of the mitral valve associated with other disturbances in 104, constrictive pericarditis in 16, and other disorders in 13. Of 238 patients with congenital cardiopathy, cyanosis was present in 81. Cardiac catheterization was carried out in 68 patients while they were under general anesthesia. In the course of cardiac catheterization, venous spasm developed in 3 patients and arrhythmia in 50. Episodes of nodal and atrial extrasystoles were common but well tolerated. Atrial fibrillation developed in 1 patient and paroxysmal tachycardia in 2. Acute pulmonary edema developed in 4 patients—in 2 during and in 2 after the catheterization. Complications after use of the catheter included chills (which developed in 19 patients), mild febrile episodes (in 75), and benign phlebitis of veins of the arms (in 8). The deaths of 3 patients, which can be attributed to use of the catheter, were related to pulmonary edema in 2 and to cardiac arrest because of anoxemia, which developed during the anesthetic state, in 1.

To minimize complications of cardiac catheterization, the author suggests the use of flexible catheters, careful sterilization of the catheter, precise premedication, application of gas narcosis and possible blood transfusions for children, and insertion of the catheter into the left basilar vein or into the saphenous vein if the basilar vein is too narrow. He also suggests infusion of apyrogenic solutions, the strict observance of asepsis, use of electrocardiograms, roentgenologic observations, and oximetry during the procedure, if possible, limiting the duration of the catheterization to as short a period as possible, and performance of the catheterization by an experienced team. Cardiac catheterization is a valuable therapeutic tool, but its application must be individualized, taking into aaccount its limitations and hazards.

Experiments on the Antituberculous Activity of Alpha-Ethyl-Thioisonicotinamide. N. Rist, F. Grumbach and D. Libermann. Am. Rev. Tuberc. 79:1-5 (Jan.) 1959 [New York].

The antituberculous activity of alpha-ethyl-thioisonicotinamide has been tested in vitro and in experimental animals. Although this compound is a derivative of isonicotinic acid, it is not a derivative of isoniazid. It has proved to be highly active both in vitro and in vivo against strains of tubercle bacilli that are resistant to isoniazid. It is 4 times more active in vivo than thioisonicotinamide, but its toxicity is not greater than that of the latter compound. Qualitatively, the effect induced by alpha-ethyl-thioisonicotinamide is similar to that of isoniazid; quantitatively, it is twice as effective as streptomycin and one-tenth as active as isoniazid in experimentally infected guinea pigs. Its toxicity in mice is only one-fifth that of isoniazid. When alpha-ethyl-thioisonicotinamide is administered by the oral route to man, it has been found in the serum in a biologically active form. The results of these studies accordingly justify the clinical trial of this compound.

Observation on the Antituberculous Effectiveness of Alpha-Ethyl-Thioisonicotinamide in Tuberculosis in Humans. G. Brouet, J. March, N. Rist and others. Am. Rev. Tuberc. 79:6-18 (Jan.) 1959 [New York].

A clinical investigation was carried out with the administration of alpha-ethyl-thioisonicotinamide in 102 patients with pulmonary tuberculosis; 73 were men and 29 were women. Fifty-seven of the patients had recent tuberculosis, and 45 had chronic tuberculosis. A thorough physical examination, roentgenologic study, and culture of sputum and of gastric washings for Mycobacterium tuberculosis had been frequently carried out in each patient. All strains of tubercle bacilli isolated were tested in vitro for susceptibility to alpha-ethyl-thioisonicotinamide, to isoniazid, and to other common antimicrobial drugs. Alpha-ethyl-thioisonicotinamide was administered orally, the usual regimen being 1 Gm. daily, or 4 tablets, given either as 2 tablets

The place of publication of the periodicals appears in brackets preceding each abstract.

Periodicals on file in the Library of the American Medical Association may be borrowed by members of the Association or its student organization and by individuals in continental United States or Canada who subscribe to its scientific periodicals. Requests for periodicals should be addressed "Library, American Medical Association." Periodical files cover 1950 to date only, and no photoduplication services are available. No charge is made to members, but the fee for others is 15 cents in stamps for each item. Only three periodicals may be borrowed at one time, and they must not be kept longer than five days. Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

twice daily or in the individual dosage of 0.25 Gm. at 6-hour intervals throughout the day. This compound was often not well tolerated and gave rise to side-effects, such as anorexia, nausea, or gastric irritation; the patients either ceased to gain weight or actually lost weight. There was no evidence, though, that it had a toxic effect on the liver, the kidneys, or the hematopoietic system, and it seemed to have a minimal neurotoxic activity, which required special attention only in patients treated concomitantly with isoniazid or cycloserine.

The treatment with alpha-ethyl-thioisonicotinamide had a beneficial effect on the clinical course, on the roentgenologic aspects, and on the bacteriological findings of patients with pulmonary tuberculosis. The bacteriostatic effect of this compound was particularly pronounced in patients with recent tuberculosis, and resolution was obtained within 2 or 3 months after institution of therapy in a large number of patients. The action of this drug, however, was not constant. The condition of some patients did not improve, and the emergence of bacterial resistance to alpha-ethyl-thioisonicotinamide occurred in several patients, but without evidence of decreased sensitivity to other bacteriostatic agents. After the administration of other orthodox antimicrobial drugs rapid improvement occurred in these patients.

Alpha-ethyl-thioisonicotinamide should not be administered alone, but only in conjunction with other antibacterial drugs, such as isoniazid, or isoniazid and streptomycin. It was found in this series that the combined treatment was very effective in patients with advanced pulmonary tuberculosis who had been treated previously, and it was active against strains of tubercle bacilli that were resistant in vivo to isoniazid and streptomycin. The authors believe, on the basis of the present experimental clinical investigation, that a study on the triple-drug regimen, consisting of isoniazid, streptomycin, and alpha-ethyl-thioisonicotinamide, is permissible in order to determine more precisely its effectiveness in patients with progressive pulmonary lesions.

Observations on the Administration of Kanamycin to Patients with Tuberculosis. K. W. Wright, A. D. Renzetti Jr., J. Lunn and P. A. Bunn. Am. Rev. Tuberc. **79:**72-77 (Jan.) 1959 [New York].

Kanamycin, a new antimicrobial drug which is effective in low concentrations in vitro against tubercle bacilli, has been administered by the intramuscular route to 11 patients with chronic pulmonary tuberculosis. The ages of the patients ranged from 9 to 57 years. Sputum cultures for acid-fast bacilli were positive in all patients, and all strains of tubercle bacilli were resistant to streptomycin, isoniazid, and PAS. The inhibitory blood concentrations were produced and maintained for 8 hours with a daily dose of 0.5 Gm. of kanamycin. Impaired hearing resulted in 2 patients after the daily administration of 1 Gm. of kanamycin. Granular casts appeared in the urine of all patients within 14 or 28 days of treatment. There was no evidence that the drug had a toxic effect on the liver, on the vestibular apparatus, or on the hematopoietic system. No significant sensitivity reaction to the drug occurred in these patients, other than eosinophilia which was common. The rapid appearance of strains of tubercle bacilli highly resistant to kanamycin suggests that in prolonged treatments this drug should be administered only in conjunction with other antituberculous agents. The disappearance of tubercle bacilli from the sputum of one patient and the favorable changes in the sputum volume, in the body weight, and in the chest roentgenograms in some patients indicate that the drug is sufficiently effective to warrant further clinical trial.

Diagnosis and Therapy of Cushing's Syndrome. A. Labhart, E. R. Froesch and W. Ziegler. Schweiz. med. Wchnschr. **89:**44-53 (Jan. 10) 1959 (In German) [Basel, Switzerland].

The authors discuss the histories of 10 patients (9 women and 1 man) with adrenal cortical hyperfunction (Cushing's syndrome) observed in the medical clinic of the University of Zurich before October, 1957. Autopsy reports were available in 2 of the cases, and in 7 patients, who had undergone adrenalectomy, the adrenals could be examined. An adenoma was found in the adrenals of 1 patient, whereas the adrenals in the other 8 patients showed hyperplasia. Although in one of these patients the hyperplasia was not detectable on naked-eye inspection, the histological examination in this and the other patients with hyperplasia revealed changes, such as adenoma-like sections in the cortex, obliteration of the cortical stratification, and cellular strands resembling fasciculated tissue. Studies on the hypophysis in the 2 autopsies revealed in one patient a basophil adenoma and in the other slight basophilism, in addition to metastases of a squamous-cell carcinoma. The excretion of hydrocortisone, ascertained on the basis of the 17-hydroxycorticoids, either was greatly increased or was in the upper limits of normalcy, but in 2 patients, in whom the aldosterone excretion was examined, reduced values were found, and one of these had hypopotassemia. The mineralocorticoids were not involved in the hypersecretion, the shifts in the electrolytes and the alkalosis being caused by the hydrocortisone.

An average of nearly 3 years elapsed between the appearance of the first symptoms and the correct diagnosis; in one patient the syndrome was recognized after 3 months. The most frequent of the clinical symptoms of Cushing's syndrome was a plethoric appearance with the characteristic

moon-face; this was observed in all 10 patients. Hypogonadism was observed in 6 of the 10 patients: 5 of 8 women had amenorrhea or oligomenorrhea, and the man had impotence and azoospermia. Obesity, particularly of the trunk, was observed in only 4 patients. Hypertension occurred in 6 patients, but it was not severe. Osteoporosis was present in 7 patients and was severe in 2. Typical red striae existed in 4 patients, and 4 others had areas of superficial bleeding. Diabetes, as evidenced in reduced sugar tolerance, existed in 8 patients. Unusual features observed in this group of patients included: a sibship with polyadenomatosis (hyperparathyroidism, islet adenoma, etc.); the occurrence of adrenal hyperplasia secondary to an invasive pituitary adenoma composed of chromophobe-basophilic-mucoid cells; and the association with bronchial carcinoma, with creatinuria and severe muscular dystrophy, with testicular atrophy, and with irreversible secondary adrenal insufficiency after operation on an active adrenal adenoma.

In addition to the cardinal symptoms, the diagnosis of Cushing's syndrome depends on the 48-hour intravenous corticotropin tolerance test with determination of the urinary steroids. Regarding the treatment, the authors say that no reliance can be placed on the rare occurrence of a spontaneous remission, the less so since untreated Cushing's syndrome is usually fatal within 5 years. Irradiation of the pituitary is sometimes effective, but the recurrence rate is high. Bilateral total adrenalectomy and subsequent substitution therapy are presently the treatment of choice of bilateral adrenal hyperplasia.

The Natural History of Tuberculosis in the Human Body: I. The Demonstrable Primary Pulmonary Infiltrate. J. A. Myers. Am. Rev. Tuberc. **79:**19-30 (Jan.) 1959 [New York].

A group of 300 children with primary pulmonary tuberculous infiltrates, ranging in age from 2 months to 20 years, were examined between May, 1921, and November, 1941. The primary infiltrates in these children varied in size from those scarcely large enough to be demonstrable to big dense homogenous areas; they were not limited to any lobe or area, some appearing even in the apexes of the upper lobe. The roentgenograms did not visualize characteristic shadows; therefore, differentiation from other diseases, even from the reinfection type of tuberculosis, was rendered difficult. After a few months the primary infiltrates began slowly to resolve, and within a year the shadow-casting lesions disappeared, except for the roentgenologic evidence of calcific deposits at the sites of the original lesion or in the hilar region or both.

Of the 300 children, 267 were followed up; 10 were not examined; and 26 had died. The cause of death was attributed to tuberculosis in 9, the disease being the acute, rapidly fatal forms in 7 (meningitis, pneumonia, and miliary dissemination); the other two patients died of chronic pulmonary tuberculosis 8 and 19 years, respectively, after the primary pulmonary infiltrate was detected. Among the 231 survivors who were examined, the reinfection type of chronic clinical tuberculosis developed subsequently in 9, but it occurred in the region of the primary infiltrate only in 1. The remaining 222 patients have no evidence of any clinical disease.

While mortality and morbidity to date may seem small, it may still be considerably increased, because the subjects under consideration have not lived the halfway mark of natural span of life. The benign character of the demonstrable primary pulmonary infiltrate is no assurance against the development of a chronic disease, because foci that continue to harbor tubercle bacilli may subsequently release organisms that result in clinical lesions.

SURGERY

The Advantages of Early Spine Fusion in the Treatment of Fracture-Dislocation of the Cervical Spine. H. F. Forsyth, E. Alexander Jr., C. Davis Jr. and R. Underdal. J. Bone & Joint Surg. **41A:**17-36 (Jan.) 1959 [Boston].

The authors report on 72 male and 9 female patients, between the ages of 8 months and 75 years, with fracture-dislocation of the cervical spine who were considered for internal fixation and spine fusion early in their course of treatment. Fifty-one of the 81 patients sustained their injuries in an automobile accident; the injuries of 12 were produced by falling, those of 6 by diving, those of 3 by gunshot, and those of the remaining 9 by miscellaneous causes. Of these 81 patients, 35 were treated with fusion and 46 were treated conservatively. Recurrence of the deformity developed in 3 of the 46 patients treated conservatively, and fusion was subsequently done. Thus, a total of 84 cases were analyzed. In the treatment of cervical spine injuries, first consideration must be given to protection of the neural structures. Relieving all pressure from the spinal cord and nerve roots and putting them at rest afford the best opportunity for return of function of the neural structures. To do this with certainty requires accurate reduction of bone structures, followed by internal fixation for immediate stability and spine fusion to prevent late recurrence. The general routine of skeletal traction, internal fixation, and spine fusion constitutes a method of treatment that needs to be varied only slightly in order to be practiced in a large percentage of all serious injuries of the cervical spine.

The results obtained in the 35 spine fusions and in the 46 injuries treated conservatively indicate that the patients in whom fusion was done had less residual deformity and a lower rate of recurrence.

In addition, less time was spent in the hospital or in uncomfortable casts, and less time was spent away from work. The mechanism of injury in fracture-dislocation of the cervical spine is discussed in some detail, with emphasis on the hyperextension fracture-dislocation which is caused by a combination of forcible extension and compression acting from above. A new interpretation of the roentgenologic findings in a large group of fracture-dislocations with mild anterior displacement showed that about 50% of them were caused by hyperextension rather than flexion as previously thought. Before this mechanism was recognized, it was difficult to understand the severe neurological changes that were frequently present. Placing these cases in the group of hyperextension injuries makes the neurological damage understandable.

Brain Abscess. C. V. M. Fog. Danish M. Bull. **5**:260-264 (Dec.) 1958 (In English) [Copenhagen].

Fog reviews 114 cases of brain abscess in 89 males and 25 females, representing all age groups. The localization was in the brain stem in only 2 cases, was supratentorial in 11, and was infratentorial in 12. In 33 cases the abscess was otogenic; in 6, rhinogenic; and in 28, thoracogenic. In 11 cases it was due to cranial injuries, in 36 to other causes. The most frequent cause was infection from the ears and nose; the next most frequent cause, infection from the lungs. The bacterium most often found in cultures from pus was Staphylococcus aureus. The mortality was highest in cases with brain abscess of thoracogenic origin. The prognosis is best for sterile abscesses and least favorable in cases with streptococci. Diagnosis may be difficult. A brain abscess may be present without demonstrable leukocytosis or choked disk. Most of the patients were treated by total excision, which was usually preferable to more conservative methods. The mortality has fallen steadily since the advent of penicillin and the introduction of rational chemotherapy, with resistance determinations as a guide in the choice among streptomycin, tetracyclines, chloramphenicol, sulfonamides, and penicillin, but it is still about 25%. Fifty-five of the 59 survivors were followed up. Six had died of other diseases. In the remaining 49, the late prognosis was found to be best for the infratentorial cases. Almost half of the patients with supratentorial abscesses had reduced working capacity.

Experience with Arterial Replacement. H. W. Scott Jr., J. A. Kirtley, R. I. Carlson and J. H. Foster. J. Tennessee M. A. **52**:1-3 (Jan.) 1959 [Nashville].

The authors report on 183 patients with vascular disease on whom arterial grafting was performed at the Vanderbilt University Hospital and the Thayer Veterans Administration Hospital in Nashville, Tenn., since 1954. A freeze-dried homologous homograft was employed in 149 patients, and a synthetic prosthesis in 34. Arteriosclerotic aneurysm of the abdominal aorta and arteriosclerotic occlusive disease of the terminal aorta were the 2 commonest indications for arterial grafting in the group of 149 patients; 21 of them died, representing a mortality rate of 14.5%. Segmental arteriosclerotic occlusion of a peripheral artery was the commonest indication for grafting in the group of 34 patients; 4 of them died, representing a mortality rate of 12%.

All the abdominal aneurysms in this series originated below the renal arteries and allowed anastomosis of the grafts, after resection of the aneurysm, without encroachment on the renal vessels. In many of the patients with arteriosclerotic occlusion of the terminal aorta (Leriche's syndrome), blood flow to the extremities was improved by employing bypass grafts from the aorta to the femoral arteries without disturbing collateral vessels in the region of the aortic bifurcation. Bypass grafts were also employed for segmental occlusions of the femoral artery. In other arterial lesions, resection and restoration of normal circulation were performed by graft implantation. The patients were followed for periods of up to 4½ years. The results were good. There was no recurrence of symptoms, and there was good maintenance of function. The incidence of thrombosis in grafts was low (5% in the group with homografts and about 10% in that with synthetic prostheses), and there was no evidence of aneurysmal dilatation of any grafts. Aortograms performed as late as 3 years after graft implantation showed maintenance of structural integrity of the arterial substance. While freeze-dried arterial homografts have functioned well, it is likely that the improved synthetic prostheses curently available will largely replace the homografts as arterial substitutes.

Prognosis in Lung Cancer Surgery Based on Blood Vessel Invasion. E.-D. Gagnon and C. Gelinas-Mackay. Canad. J. Surg. **2**:156-160 (Jan.) 1959 [Toronto].

At Notre-Dame Hospital in Montreal during the 9 years from 1949 to 1957, a total of 329 cases of lung cancer were diagnosed, of which 254 were histologically verified by bronchoscopic examination, biopsy of lymph nodes, thoracotomy, or autopsy. In only 77 (30%) of the verified cases was a surgical attempt at cure possible. Of the 77 patients, only 48 could undergo resection. Eleven of these died within 30 days after surgery, leaving 37 who could be followed up. The surgical specimens of these 37 survivors were studied, special attention being given to the invasion of the blood vessels. All patients surviving and "well" for more than 2 years had no blood vessel invasion in the removed lung, and patients dying of other causes likewise

had no blood vessel invasion. However, all but one of the patients dying of metastases had blood vessel invasion.

The obliteration of lung vessels by proliferation of the intima seems to be an effective barrier against metastases. The histological type of the carcinoma does not seem to influence the prognosis directly. The presence or absence of blood vessel invasion, more than any other criterion, seems to be important in the prognosis of lung cancer. More attention should be paid to this as an aid to prognosis. Operation at the earliest possible time affords the only chance of cure.

Carcinoma of the Stomach: Follow-Up Investigation in 451 Cases. M. Andreassen. Danish M. Bull. **5**:264-268 (Dec.) 1958 (In English) [Copenhagen].

The material comprises 451 cases of carcinoma of the stomach in 319 men and 132 women who were treated from 1945 to 1955 in the Rigshospitalet, Copenhagen. The disease occurred predominantly in the 5th and 6th decades of life. Four patients were under 30 years of age; in such cases the prognosis is usually less favorable, because at this early age the diagnosis of cancer is often overlooked. Only 40 patients sought treatment within 3 months after the development of symptoms. Radical operation was performed in 211 cases, or 47%, with a 3-year survival rate of 21%. The author stresses the importance, in surgical treatment of cancer of the stomach, of more extensive employment of histological examination of the edges of the resection during the operation, with meticulous removal of the lymph nodes and fat from the stomach bed, especially from the hepatic pedicle. Possibly total gastrectomy can be employed to a greater extent if supplemented by an intestinal reservoir introduced between the esophagus and the stomach. Increased palliative resection is recommended in cases in which the tumor cannot be removed radically.

A Contribution to the Knowledge of Saint's Triad (Hiatal Hernia, Gallstones, and Diverticulosis). E. Fedele and L. Sabatini. Policlinico (sez. chir.) **65**:243-253 (Oct.) 1958 (In Italian) [Rome].

The authors report on 2 women, 44 and 52 years of age, with Saint's Triad, who were observed at the surgery clinic of the University of Rome during one year. The first patient 4 years before observation felt some pain in the epigastric region. This symptom became more intense and more frequent. No direct relationship between the pain and the digestion was apparent. The patient complained also of a burning sensation in the retrosternal region, which became more severe during hiccups. Difficulty in the digestion of especially fatty foods occurred 2 years before observation; half an hour to 2 or 3 hours after meals the patient suffered pain which originated in the epigastrium and extended to the right of the hypochondrium. One year before observation occasional diarrhea, with semiliquid feces at times mixed with mucus, was noted. Roentgenologic examination showed a hiatal hernia of the sliding type at the fundus of the stomach, and diverticula were seen in the cecum, in the transverse colon, and at the hepatic flexure of the colon. Cholecystography showed 2 transparent calculi at the fundus of the gallbladder. The second patient complained of pain, vomiting, and, rarely, some fever for 14 years before coming to the clinic; these symptoms became more frequent with time. Two years before observation she suffered a sensation of burning in the retrosternal region. Over the years she had made frequent use of laxatives. A large swelling could be felt in the iliac fossa on the right. Roentgenologic examination showed a gastroesophageal reflux; the lower part of the stomach appeared partially herniated through the esophageal hiatus. A mass, the size of a big orange, was noted in the small intestine. Diverticula were seen in the ascending and the transverse colon, and gallstones were noted in the gallbladder.

The authors think that what is usually referred to as Saint's Triad is a syndrome, and that the presence of the 3 pathological manifestations (hiatal hernia, gallstones, and diverticulosis) is a mere coincidence and is not due to a common cause. The association and the interrelation of the manifestations are worthy of investigation in order to remove the lesion which is most responsible for the syndrome.

GYNECOLOGY & OBSTETRICS

Exchange Transfusion in Treatment of Septic Toxemia Due to Clostridium Perfringens. G. Villavicencio G., A. Hille and C. Paredes. Obst. y ginec. latino-am. **16**:255-265 (July-Aug.) 1958 (In Spanish) [Buenos Aires].

Eight women with septic toxemia due to Clostridium perfringens after an induced abortion were observed during 1957-1958 at the San Borja Maternity Hospital of Santiago, Chile. The patients were hospitalized 48 to 96 hours after the induced abortion. They were in acute shock (2 being in a condition of irreversible shock), with severe hemolytic anemia, marked hemoglobinemia and hemoglobinuria, jaundice, and uremia with marked oliguria or anuria. During the first day of hospitalization the patients were treated by curettage and administration of antibiotics and perfringens antitoxin, and received a direct transfusion of from 8 to 10 liters of fresh blood. The technique was the same as that used in an indirect transfusion with fresh blood, the injection being given into the cephalic

or the jugular vein. Uremia, creatinemia, and uricemia diminished in 2 or 3 days, and diuresis reappeared after the first exchange blood transfusion in 3 out of 5 patients. In the other 2 patients a second transfusion of the same quantity of fresh blood was necessary 4 days after the first for obtaining satisfactory results. One patient had 3 such transfusions during a 24-day period of anuria; diuresis reappeared after the third and last transfusion. The results show recovery of the patients in 75% of the cases. The authors conclude that exchange blood transfusion should constitute a routine treatment of septic toxemia due to perfringens after an induced abortion, being given at the same time that antibiotics and perfringens antitoxin are.

Fluoxymesterone (Halotestin) in the Treatment of Advanced Breast Cancer. K. B. Olson. New York J. Med. **59**:248-252 (Jan. 15) 1959 [New York].

Fifteen women, between the ages of 39 and 72 years, with advanced cancer of the breast, were treated with a new halogenated corticosteroid, fluoxymesterone (Halotestin). Thirteen of the 15 patients had previously undergone radical mastectomy, and 8 had been treated previously with either androgens or estrogens. Two patients were premenopausal and had previously been castrated without remission of their disease. One patient was treated on exacerbation of her disease after a remission resulting from hypophysectomy. Fluoxymesterone was initially administered in doses of 10 mg. per day orally. This dose later was increased in all patients to 20 mg. daily. Subjective improvement of some degree, consisting of a sense of well-being, increase of appetite, and a decrease of pain, occurred in 6 patients. Objective improvement, as measured by healing of skeletal lesions and reduction of the size of lymph nodes by more than 50%, occurred in 4 of these 6 patients. The patient who previously had a hypophysectomy had a short objective remission. The 2 menstruating patients who failed to respond to surgical castration likewise failed to respond to fluoxymesterone therapy. Eight patients received no benefit from fluoxymesterone therapy, and all of them subsequently died. Two of the 4 patients with objective improvement died. The usual effects of androgenic hormones were noted in most of the patients continuing therapy for more than one month, as evidenced by hirsutism, acne, increased libido, edema, and increased erythropoiesis, but the impression was gained that these effects were slower to occur and were not of such magnitude as those with testosterone propionate and methyltestosterone.

Fluoxymesterone appears to be a potent androgen and capable of producing objective remission in advanced breast cancer. It has the advantage of being administered orally and is well tolerated in effective doses. It is not known whether doses of more than 20 mg. per day will be more effective, but no remissions were noted with doses lower than that amount. It seems probable that fluoxymesterone is at least as good as other effective androgens and deserves further trial.

PEDIATRICS

Phenylketonuria: An Unusual Case. S. A. Leonard and F. L. McGuire. J. Pediat. **54**:210-214 (Feb.) 1959 [St. Louis].

The authors report on an 8¼-year-old girl with phenylketonuria. Physically the child was relatively normal except for her height (47½ in. [120 cm]), which was below the 16th percentile; her weight was normal. Psychological evaluation revealed an intelligence quotient of 70, which would place her within the borderline mental deficient category. Her serum phenylalanine level was 36.5 mg. per 100 cc. and thus did not correlate with her IQ. A routine ferric chloride test gave positive results. The child was found high in ability for rote memory, and it was felt that increased mental age might be obtained with continued environmental security. She was not treated with low-phenylalanine diet because of poor experimental results in older children; in addition, she was asymptomatic. A brief review of the literature showed that the first descriptions of phenylketonuria were all those of severe mental retardation. Psychologically this child was found to be a "phenylketonuric" and not a "phenylpyruvic oligophrenic." The authors believe that "phenylpyruvic oligophrenia" is no longer a correct term for the syndrome of phenlyketonuria, and that the report of this patient may add stimulus to the broadening of the spectrum of phenylketonuria.

Thyroid Cancer in Children. J. R. Moore and A. D. McKenzie. Canad. J. Surg. **2**:175-179 (Jan.) 1959 [Toronto].

The authors present the histories of 6 children with thyroid carcinoma, who were observed in the Vancouver area between 1952 and 1957 inclusive. Malignant thyroid tumors in adults were likewise reviewed, and it was found that children accounted for 5% of the group. The children ranged in age from 7 to 17 years, and all but one were boys. That thyroid carcinoma in children is not readily suspected is proved by the fact that in 4 of the children symptoms had been present for from 5 to 18 months. The other 2 children had symptoms for one month each. The finding of a thyroid nodule or nodules in children is more serious than in an adult, and the majority are likely to be carcinoma. It can be expected that the presence of masses in the neck will be the initial sign. As with papillary carcinoma in adults, a considerable number of children will have

metastatic lymph node involvement when they are first seen. There were 4 such patients in this series, and one of these had lymph node enlargement as the only clinically demonstrable lesion. Only 2 of the 6 patients had localized thyroid nodules, both on clinical examination and at operation.

Histologically, 5 patients had a papillary adenocarcinoma, while the remaining patient had a papillary follicular type of lesion. Since 1950 there have been several reports on previous irradiation in children who later developed cancer of the thyroid. All 6 of the patients in this series had received irradiation for an "enlarged thymus gland" during infancy. The total dosage in each instance was about 500 r. Surgical excision was the primary treatment in all the patients. External irradiation was used in 2 patients, in one of whom local removal was not complete. Radioiodine (I^{131}) was helpful in one patient. The 2 children with the localized disease are well with no clinical evidence of recurrence, one after 5 years. Residual or recurrent disease is present in the other 4 patients.

A Contribution to the Knowledge of the Christmas Factor Deficiency in Infants. W. Felici and V. Bacchetta. Minerva pediat. **10**:1226-1234 (Nov. 3) 1958 (In Italian) [Turin, Italy].

The authors discuss the histories of 2 children with deficiency of the plasma thromboplastic component (Christmas factor). The first child, at the age of 3½ years, had developed a swelling of the left knee because of a fall. The swelling persisted unchanged and painful for 25 days. During the following 2 years the condition improved only upon immobilization of the joint and returned to the initial state whenever attempts to move the knee were made. The child was brought to the hospital at the age of 6, and a diagnosis of hemophilia was made. One month before the last observation he had suffered a gingival hemorrhage. Moreover, owing to trauma to the left gluteal region incurred in a fall, he had developed a hematoma in the same region, with pain radiating into the thigh and the left popliteal region; the swelling regressed slowly and disappeared after 20 days. Coagulation tests gave normal results. The authors believe that hemophilia in this patient, who was the only male child in his immediate family, was hereditary. In taking the history it was revealed that a maternal uncle, at the age of 2 years, had had a profuse hemorrhage caused by a lacerated and contused wound on the forehead; later this relative suffered from rheumatism of the major joints and died at the age of 17 of unascertained causes.

The second child, who died after 2 days of life, showed at birth hemorrhage and plasma thromboplastic component (PTC) deficiency associated with prothrombin and factor VII deficiencies. The brothers of the child had not experienced any hemorrhages. The authors believe that in this child the PTC deficiency, combined with a deficiency of prothrombin and factor VII, was to be considered the result of disturbances in the production of coagulation factors of the plasma by the liver. Such disturbances are frequent in the neonatal age. The diagnosis of a hemophilic syndrome was excluded in this case, inasmuch as the PTC deficiency was not the result of a hemophilia-like disease (Christmas disease), which would imply the operation of hereditary influences, but was the result of functional immaturity or parenchymal alterations in the liver.

DERMATOLOGY

Cryoglobulins in the Chronic Lupus Erythematosus. T. Chorazak. Acta dermat.-venereol. **38**:322-328 (no. 5) 1958 (In English) [Stockholm].

The author points out that the obscure etiology of the collagen diseases has led to explorations going beyond the dermatological field, being concerned with such factors as the erythrocyte sedimentation rate, the detection of L. E. cells (Hargraves' sign), and the investigation of the protein pattern of the blood serum. Investigators who studied the blood serum proteins by means of paper electrophoresis in dermatological conditions, and particularly in lupus erythematosus, found that there is a reduction in albumin and an increase in globulins, particularly the gamma globulin fraction. Cryoglobulin (Lerner and Watson's term [1947]) for a blood globulin precipitating in serum at a temperature of from 7 to 11 C [44 to 52 F] is also known as the "cold fraction." Even the presence of small amounts of cryoglobulins is pathological and is classified by the author as a paraproteinemia. Earlier investigators had demonstrated that the electrophoretic velocity of cryoglobulins is similar to that of gamma globulins and perhaps of beta globulins or lies between beta and gamma globulins.

The author investigated the presence of cryoglobulins in the serum of patients with chronic lupus erythematosus and found this "cold fraction" in 48 of 72 patients (67%). He regards this as an extremely high percentage, the more so since others, in examining the serums of 40 healthy subjects, never found cryoglobulins, and he himself failed to find them in 12 persons who were healthy or had only minor skin lesions. Practically all the 72 patients showed hyperglobulinemia, particularly of the gamma and less so of the beta fraction. Of 44 patients with hypergammaglobulinemia, 29 had cryoglobulins. Of 27 patients with hyperbetaglobulinemia, only 17 had cryoglobulins. The author feels that the high incidence of cryoglobulinemia in the patients with chronic lupus erythematosus suggests that this factor has some connection with the pathogenesis of the disease; at any rate, the presence of cryoglobulins cannot be regarded as of no importance, because it usually accompanies

serious diseases. The site of formation of cryoglobulins is still controversial; some believe they are formed in the liver, and others in the muscles, in the reticuloendothelial system, in the mast cells or the plasma cells.

No correlation could be found between cryoglobulinemia and the severity of lupus erythematosus, although in 7 patients who had hyperglobulinemia, but no cryoglobulins, the local lesions had healed (thin, smooth scars with pigmented borders but without erythema, infiltration, or sealing). The lack of uniformity of the electrophoretic aspects of patients with lupus erythematosus permitted no definite conclusions. Hyperglobulinemia, with high values of gamma and beta fractions, was found to persist both in active lesions and in locally cured ones. Some observations on the patients studied by the author suggested that the cryoglobulins might be connected with the transition from a chronic to an acute form of lupus erythematosus, with increase in body temperatures, superficial ulcerations on hands and feet, pain and edema in the joints. Corticotropin and cortisone have been observed to cause partial or complete disappearance of cryoglobulins, and it is suggested that this mechanism might be responsible for the beneficial effect of these hormones in lupus erythematosus.

Plantar Wart Treatment with Ultrasound. H. Kent. Arch. Phys. Med. **40**:15-18 (Jan.) 1959 [Chicago].

This report is concerned with the use of ultrasonic wave lengths in the treatment of plantar warts. The equipment used in all treatments was a Birtcher Ultrasonic Model No. 105-F, having a frequency of 1 megacycle. The transducer or soundhead is able to deliver a total energy of 0.5 to 15 w. The crystal contained in this transducer is 5 sq. cm. in area and is designed to deliver an output of 0.1 to 3 w. of ultrasonic energy per square centimeter. The coupling medium used on all patients was liquid petrolatum (white mineral oil) U. S. P., a low viscosity fluid which also acts as a lubricant, so that all areas of skin are kept in contact. A gentle firm pressure of the soundhead was maintained during treatment and a rotatory motion employed. The duration of treatment was arbitrarily kept to 15 minutes. With this technique, no complaints were received concerning heat effects or pain. On the contrary, when a wart had been painful, almost complete relief was obtained after the first 5 minutes of treatment.

Nine patients were treated. As a rule, single, discrete, recent plantar warts were preferred. Two patients had multiple warts. The frequency of treatments varied from a single to 11 courses. Of the patients described, one had previously been treated with maximum x-ray doses on isolated warts on both feet. The warts were approximately 2 mm. in diameter, circumscribed by fibrous tissue, and only slightly elevated from the surrounding skin. Bunion pads had been employed because the warts were quite painful. Only the lesion on the left foot was treated with ultrasonic waves. The wart on the right foot served as a control. After the 8th dose, the wart appeared to become more elevated. Pain recurred, but after the wart was sanded down with emery paper, comfort was restored. The lesion became smaller until finally a minimal scar remained. Six months later, the treated wart had not recurred, whereas the wart on the untreated foot remained unchanged.

The general results suggest that ultrasonic therapy is nearly always effective in the treatment of plantar warts. Pain is relieved almost immediately, followed by necrosis of the wart. Normal skin is unharmed by the technique. Changes evoked in these warts suggest either a vascular, a molecular, or a viral effect. Advantages of ultrasonic therapy of plantar warts include quick pain relief and the fact that it involves neither paring nor skin destruction nor scarring nor protective pads, that the patient remains ambulatory, that single warts in difficult locations (edge of heel) can be treated, and that recurrences are apparently prevented.

PUBLIC HEALTH

Report on Edinburgh X-Ray Campaign, 1958: Introduction and Community Arrangements: Technical and Administrative Arrangements: Results of Campaign. H. E. Seiler, A. G. Welstead and J. Williamson. Tubercle **39**:339-359 (Dec.) 1958 [London].

The authors report on an x-ray campaign conducted in Edinburgh in 1958. A cooperative effort by local authority, local hospital authority, and the central department of health, with the good will and help of local community workers, achieved an 84.4% response of the public to the request to have chest x-rays taken. The technical and administrative arrangements proved adequate but only as a result of detailed previous planning. Four hundred twenty-three new patients with active pulmonary tuberculosis were found. The highest prevalence of active tuberculosis was in males over 60 years of age (3.30 per 1,000). The over-all prevalence in males was 2.17 and in females 1.01 per 1,000 persons x-rayed. The importance of older men in the epidemiology of tuberculosis has once again been emphasized. It is noteworthy also that in these men the prevalence of carcinoma was as high as 2.34 per 1,000. It is concluded that an x-ray campaign of this sort is a useful and justifiable method of case finding for tuberculosis and other serious chest diseases. It is particularly suitable in communities where tuberculosis appears to be coming satisfactorily under control, and it may advance the day of final conquest of the disease by several years.

BOOK REVIEWS

The Effect of Advancing Age upon the Human Spinal Cord. By L. Raymond Morrison, M.D., with collaboration of Stanley Cobb, M.D., and Walter Bauer, M.D. Cloth. $6. Pp. 127, with illustrations. Published for Commonwealth Fund by Harvard University Press, Cambridge 38, Mass.; Oxford University Press, Amen House, Warwick Sq., London, E.C.4, England, 1959.

It is regrettable when it is not possible to write a favorable review of a book published posthumously. Unfortunately, this book fails in the purpose for which it was written; the changes in the spinal cord which result from advancing age are not presented in an intelligible manner. The material on which this study was based has been poorly chosen. These spinal cords were taken from the bodies of persons who died from a variety of systemic diseases such as rheumatic heart disease, lupus, ulcerative colitis, lymphoblastoma, and uremia. At least two of the patients had a pyramidal tract lesion, and at least one of these was from cerebral infarction. The reader is not informed as to the cause of death in all of the patients, nor is he given any information by means of which he might discriminate between the anatomic changes produced by aging and those resulting from disease processes. The author does not attempt to make such a differentiation, and one doubts if such could be made with accuracy on this material. It is surprising to learn that "The brains were not examined in this series." Even the changes which were observed have not been organized in a systematic fashion, and no clear-cut picture is presented of the changes produced by advancing age.

The poor sentence structure and unfortunate choice of words are striking. This monograph has been published with the aid of money from a fund established to support scientific research. The lack of a scientific approach to the problem in hand is disturbing. As if to expand a very short text into a book of even this small size, the publisher has resorted to extremely wide margins and to the use of illustrations two and three times as large as they need to be. Only the first 52 pages of this book are devoted to the subject of the title. The rest consists of an atlas of sections, stained by the Weigert and Nissl methods, of a "normal spinal cord" removed from a 24-year-old woman who died of subacute bacterial endocarditis with an occasional focus of abnormality within the spinal cord. The Weigert preparations are in no way unusual, while the sections stained by Nissl's method are reproduced at such a low magnification as to be of little value. There is no index.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

Cancer. Volume 2, Part II: Pathology of Malignant Tumours. Volume 3, Part III: Additional Pathological Aspects; Part IV: Geography of Cancer; Part V: Occupational Cancer; Part VI: Cancer Education; Part VII: Cancer Detection. Edited by Ronald W. Raven, O.B.E., T.D., F.R.C.S., Joint Lecturer in Surgery, Westminster Medical School, University of London, London. Cloth. $18 per volume. Pp. 641, 25, with 357 illustrations; 483, 18, with 165 illustrations. Butterworth & Co., Ltd., 88 Kingsway, London, W. C. 2, England; 1367 Danforth Ave., Toronto 6, Canada, 1958.

Cancer. Volume 4, Part VIII: Clinical Aspects. Edited by Ronald W. Raven, O.B.E., T.D., F.R.C.S. Cloth. $126 per set of 7 volumes. Pp. 532; 23, with 173 illustrations. Butterworth & Co., Ltd., 88 Kingsway, London, W. C. 2, England; 1367 Danforth Ave., Toronto 6, Canada, 1958.

The first volume of this six-volume British compilation on cancer was reviewed in THE JOURNAL of the American Medical Association for March 8, 1958, page 1257. The review was favorable and concluded that every investigator and student of cancer should have access to the work. This opinion is hard to maintain after the examination of these three subsequent volumes. Volumes 2 and 4 deal with human cancer by the major anatomic sites of the neoplasms, volume 2 being on pathology and volume 4 on clinical aspects. This separation is unattractive to this reviewer, particularly since radiotherapy is relegated to the forthcoming volume 5. As a result, for carcinoma of the uterine cervix, pathology is to be found in volume 2, certain clinical features in volume 4, radiotherapy in volume 5, and cytodiagnosis in a section of a chapter in volume 3. The presentation of this and other important human neoplasms becomes choppy, closely interrelated aspects are torn apart, and some important considerations are barely touched on while others are unnecessarily duplicated.

Volumes 2 and 4 are written almost entirely by British authors. In general, the concepts and practices of pathology and of clinical management of cancer do not differ significantly from those of a similar cross-section of authorities who might have been selected in the United States. Differences do appear, however, more related to individual experiences than to national practices. For example, the editor contributes a 20-page chapter on the clinical aspects of breast cancer. The advice regarding treatment is, for clinical stage 1, radical mastectomy and postoperative radiation; for clinical stage 2, preoperative radiation followed by radical mastectomy. "Oophorectomy should be performed for all premenopausal patients . . . irrespective of the stage of disease." These recommendations would not be in agreement with the practices of many other centers. No other views are presented; the recommendations are not supported by

the limited statistics on end-results from the Royal Marsden Hospital; and that is all that is said about prognosis. In contrast, one whole page and 4 of 31 references are devoted to adrenalectomy and hypophysectomy, with the prospectus for volume 6 indicating additional separate chapters on each of these subjects.

The first chapter of volume 4 presents the subject of staging and emphasizes a "TNM" system that is still under discussion as a possible standard. It seems odd that no special consideration is given to end-results, survival analysis, or the duration of cancer among "untreated" patients, particularly since Great Britain has been the first to use biometric surveys and has some excellent regional and national cancer registries.

Volume 3 is divided into five main parts, including additional pathological aspects, geography of cancer, occupational cancer, cancer education, and cancer detection. The 23 chapters by 22 authors are of widely different quality, and the collection displays a lack of over-all editorial integration. The chapter on tissue culture is good, but it is directed to the growth of cancer cells, which obscures the recent difficulties in separating "normal" from "neoplastic" cells under conditions of in vitro culture. The chapter on neoplasms in domesticated animals should have been either much longer or much shorter. It has the appearance of editorial dissection, leaving some sections misleading in their incompleteness, and retaining such trivial data as a list of the most popular breeds of dogs in Great Britain and the United States. The best chapters in volume 3 are on the epidemiology of cancer, and this reviewer would have liked to have a whole volume devoted to these studies. The reports by Stocks, Dorn, and Clemmesen are particularly noteworthy, yet nowhere is it made clear that these population-based incidence analyses should not be compared directly with the relative distribution frequency studies from India and South Africa. The excellent chapters on occupational cancer of the skin and urinary bladder and leukemia could well have been extended to include occupational neoplasms of the lung and upper respiratory passages.

Cancer education is treated in chapters that appear to be essentially promotional progress reports of the sponsoring agencies. Only the paper by Wakefield presents the philosophy and the limitations of this field of endeavor. The two chapters on cancer detection, by O'Donnell and Day, are thoughtful, complete descriptions of more than passing value.

These three volumes, it is regretfully concluded, compare badly with several other textbooks on cancer. In the field of research "The Physiopathology of Cancer," edited by Homburger and Fishman, is certainly a more intelligently gathered collection, while for the clinical-pathological aspects "Cancer," by Ackerman and del Regato, retains its place as the best source in English. Knowledge about cancer is so incomplete that anything approaching a systematic compendium is an impossibility. The best that can be done is to collect the views of the recognized leaders in the field, without the illusion that these views are necessarily correct. Under these circumstances it might be desirable to print on the cover of such compilations of cancer data a warning to the reader, such as "Opinions contained herein are those of the authors and do not necessarily reflect the truth, especially when such opinions are presented as facts."

History of the Second World War: United Kingdom Medical Series. Editor-in-chief: Sir Arthur S. MacNalty, K.C.B., M.A., M.D. The Royal Air Force Medical Services. Volume III: Campaigns. Edited by Squadron Leader S. C. Rexford-Welch, M.A., M.R.C.S., L.R.C.P. Cloth. 105 shillings. Pp. 730, with illustrations. Her Majesty's Stationery Office, Atlantic House, Holborn Viaduct, London, E. C. 1, England, 1958.

This is the third and final volume of the Royal Air Force portion of the medical history of World War II. The volume consists of 721 pages, containing discussions of the principal campaigns in which the Royal Air Force participated. There are 67 plates, 58 maps, and 37 figures. The medical activities of the RAF are covered in 11 campaigns, extending geographically from the equator to the Arctic Circle. Medical conditions varied greatly, as one would expect, the problems of northern Russia being far different from those of equatorial Africa.

The plans made for continental Europe in 1939 had to be discarded after the destruction of the entire Polish Air Force in the first 48 hours of the invasion of Poland, and it became necessary to disperse all units. At times air squadrons were split up between air fields 30 miles apart, making executive and medical administration difficult. In addition, the weather during the winter of 1939-1940 was severe and temperatures fell at times to below 0 F. The losses due to enemy action from Sept. 3, 1939, to June 19, 1940, totaled 407 deaths and 632 wounded. The average strength during this period was 15,172, with an average number of casualties of over 48 hours' duration of 28.3 per thousand.

The Norwegian expedition was undertaken at short notice with little or no preparation. It was short-lived, however, and lasted only from April 20 to June 8, 1940. The campaign in Libya and Tunisia was a difficult one, operations commencing with the initial Italian advance into Egypt in 1940. Prior to this the RAF had several peacetime garrisons in Egypt with a strength of nearly 6,000. The provision of an adequate water supply in the desert was extremely difficult, due to both scarcity and poor quality. At times the troops were issued water with a saline content of 1,700 ppm. In certain places malaria was endemic. A condition known as "desert sores" was common; these were indolent

ulcers of undetermined cause. Dysentery, typhoid, infectious hepatitis, typhus, and relapsing fever all occurred in the command.

It was during the Middle East campaign that air evacuation of sick and wounded was initiated. In March, 1941, the Australian government indicated its willingness to provide, staff, and maintain an air ambulance unit consisting of three converted DH-86 airplanes. Meanwhile, the RAF and the South African Air Force had converted a few airplanes, so that by November, 1941, 8 or 10 air ambulances were available for duty in the Middle East.

In the Greece and Crete campaign (1940-1941) suitable sanitary conditions were difficult to maintain. On Crete the RAF had its first encounter with air-borne troops as the Germans landed about 7,200 men on the first day. This number was augmented later and caused the withdrawal or capture of all British. The 151st RAF wing served in north Russia from September to November of 1941. There was little sickness in this command. Malta, West Africa, Italy and the Balkans, India, and the Far East were also the sites of RAF campaigns as was, of course, continental Europe prior to the liberation. The book is well written and easy to read. The only confusing thing to an American reader is the use of initials instead of complete names of units, installations, and activities. A glossary would prove useful.

Practical Blood Grouping. By F. Stratton, M.D., D.Sc., D.P.H., Director, Blood Transfusion Service, Manchester, and P. H. Renton, M.D., B.Sc., Deputy Director, Blood Transfusion Service, Manchester. Cloth. $9. Pp. 331, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1958.

This is the second book on blood grouping techniques that has been published in England in recent years. This book is more than a dry presentation of methods, since it gives a coherent account of blood group serology, and each point that is made is illustrated by a brief case history. Included in the book are 74 such cases, which enliven the presentation. The usefulness of this excellent review of blood group methodology, however, is seriously impaired by the inclusion of the same misconceptions and mistakes which have stigmatized the literature on blood groups for more than a decade. To mention only a few examples the authors cite with seeming approval the recent numerous investigations purporting to show an association between particular A-B-O groups and disease but fail to mention any of the criticisms which have been leveled against these reports by Wiener, Manuila, and others. The authors again cite as an established fact the highly questionable reports of rises in Rh antibody titers during pregnancy in sensitized Rh-negative women carrying Rh-negative babies.

The report of W. Weiner on the supposed anti-e specificity of autoantibodies tested by him, though poorly documented, has been widely accepted; and the authors of this book claim to have found a similar case of autoantibodies of anti-C+e specificity, although the flimsy evidence presented on page 242 appears to contradict rather than support this conclusion. The claims of anti-e specificity of autoantibodies by many other workers, not including A. S. Wiener, following the original report of W. Weiner, are reminiscent of the unsubstantiated claims of serums of anti-d specificity after Fisher's announcement of his "predictions." Probably, for every dozen reports of autoantibodies of anti-e specificity, there has been at most a single bona fide case.

On page 154, the authors again repeat the myth of the six Rh antigens C, D, E, c, d, and e. Moreover, they write, "Wiener considers that there are 8 alleles at a single locus so that the antigens . . . are determined in threes by a single gene." This is incorrect, since the myth of triple inheritance also was originated by C-D-E adherents. Wiener maintains instead that Rh agglutinogens are each characterized by multiple blood factors, ranging up to 10 factors for certain agglutinogens at the present stage of knowledge, and increasing as new Rh-Hr antibodies are found. The authors also assert that there are in use three different notations for the Rh-Hr types, namely, the C-D-E notations, the Rh-Hr notations, and "the so-called clinical notations much used in Great Britain." However, the so-called clinical or shorthand notations are nothing more than an adaptation of Wiener's Rh-Hr nomenclature, so that there are actually two, not three, nomenclatures in use. Thus, the objection to the Rh-Hr nomenclature being too difficult to understand implies that Wiener's Rh-Hr notations become more understandable only after they are renamed "clinical or shorthand notations."

In view of these faults the book regrettably cannot be recommended to beginners, because it is far more difficult to unlearn incorrect teaching than it is to learn a subject correctly in the first place. Fortunately there are more reliable books available at the present time, with whose aid beginners can readily orient themselves in this complex but important subject.

Clinical Chemistry in Practical Medicine. By C. P. Stewart, D.Sc., Ph.D., Reader in Clinical Chemistry, University of Edinburgh, Edinburgh, and D. M. Dunlop, B.A., M.D., F.R.C.P., Christison Professor of Therapeutics and Clinical Medicine, University of Edinburgh. Fifth edition. Cloth. $6.75. Pp. 342, with 30 illustrations. E. & S. Livingstone, Ltd., 16 and 17 Teviot Place, Edinburgh 1, Scotland; [Williams & Wilkins Company, 428 E. Preston St., Baltimore 2], 1958.

The number of editions this short English textbook has gone through suggests that it is a useful book to at least some members of the medical profession. As the title indicates, it is a synopsis of

laboratory examinations in clinical medicine. A chapter is devoted to each subdivision (e. g., cerebrospinal fluid and hepatic function), and each chapter consists of a short discussion of basic physiology, followed by a list of the more important tests and the principal changes encountered in disease. The material presented is accurate and up to date, and it is well and simply written, an almost universal virtue of English textbooks. The only defect of this book is its brevity; it is too synoptic. Too much has been left out, and what is presented is given in too short a manner to make it effective. For example, 14 pages are devoted to the basal metabolic rate. Three or four sentences are given to protein-bound iodine (PBI), and the subject is then dismissed with the remark that it is not suitable for routine work. In listing the causes of low glucose concentration in the spinal fluid, no mention is made of diffuse meningeal carcinomatosis. In the chapter on hormone abnormalities almost nothing is said of normal or pathological blood and urine values for the hydroxycorticosteroids, although three pages are given to the 17-ketosteroids. This book is not suitable for medical students or for physicians who want a thorough knowledge of the subject. It will certainly be useful to students of biology and biochemistry and will probably prove satisfactory for candidates for professional examinations who want a quick review of a very important subject.

Occupational Allergy: Lectures Held During a Course on Occupational Allergy at The Hague in May, 1958, Organized by the Netherlands Society of Allergy in Co-operation with the Netherlands Institute for Preventive Medicine and the Netherlands Society of Occupational Medicine Under the Auspices of the European Academy of Allergy. Cloth. $10. Pp. 329, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; H. E. Stenfert Kroese N. V., Leiden, Netherlands, 1958.

About 40 authors, including allergists, internists, pediatricians, rhinologists, and dermatologists, among others, contributed to this volume. Essentially, the book discusses various allergic manifestations produced by occupational duties, methods of allergic examination, diseases and their causes in the various professions and industries, therapy, prophylaxis, and socioeconomic aspects. Among the occupations discussed are those of wool textile workers, bakers, printers, nurses, wood workers, cement workers, miners, and employees in pharmaceutical industries. While the material is informative and may be helpful to European physicians, it is inadequate for the American physician, who is faced with problems involving plastic, petroleum, rubber, and all the complexities of a variety of chemical industries. The book lacks organization, as shown by an unevenness in the different contributions as to the factual material, form of presentation, and form of references (presence or absence of references, with or without titles, last name or first name first, full name or initials, and many errors in the spelling of names). Despite imperfections this volume can serve as a supplement to a library on occupational allergy.

Handbook of Histopathological Technique (Including Museum Technique). By C. F. A. Culling, F.I.M.L.T., F.R.M.S., Chief Technician, Westminster School of Medicine, University of London, London. With foreword by R. J. V. Pulvertaft, O.B.E., M.D., F.R.C.P. Cloth. $9; 45 shillings. Pp. 446; 27, with 80 illustrations. Butterworth & Co., Ltd., 88 Kingsway, London, W. C. 2, England; 1367 Danforth Ave., Toronto 6, Canada, 1957.

To write a handbook of histopathological technique is a difficult undertaking, in this time of rapid advances. The author has composed a remarkably inclusive book based on his many years of extensive experience in this field. The work is devoted essentially to the fundamentals of histopathological technique, and the author does not attempt to cover many of the procedures involved in histochemistry. Of particular importance, and not covered in other existing works of this kind, is a section on museum technique. Another section deals with the microscope and various aspects of microscopy, including fluorescent microscopy, polarizing microscopy, and phase-contrast microscopy. The author has produced an excellent coverage of the fundamentals of histopathological technique. His emphasis on fundamentals, with the purposeful exclusion of many techniques in histochemistry, has added to the value of this work, which should prove extremely helpful to the student.

Problems of Addiction and Habituation. Edited by Paul H. Hoch, M.D., and Joseph Zubin, Ph.D. Proceedings of forty-seventh annual meeting of the American Psychopathological Association, held in New York, February, 1957. Cloth. $6.50. Pp. 250, with 12 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W. C. 1, England, 1958.

This book consists of 15 articles and 2 discussions by various authors. Most of the articles review work already published elsewhere. The subjects of various articles cover a wide range, from the development of experimental neuroses in animals to the factors relative to social and psychiatric management of addiction in the United States. Tiebout makes an eloquent plea for direct treatment of the symptom of alcoholism; Masserman attempts to review an enormous mass of work on the effects of drugs on various forms of behavior in animals; Speer defends the use of severely repressive legal measures in the management of narcotic addiction; while Bowman favors a permissive system for the management of addiction in the United States, similar to the plan developed by the New York Academy of Medicine. As might be expected, the quality of the various articles is uneven. The book should be of most value to persons working with the problem of alcoholism or drug addiction.

QUESTIONS AND ANSWERS

ESTROGENS AND CLOTTING

To the Editor:—*If estrogens are given intravenously to control hemorrhage by quickly increasing the concentration of prothrombin and accelerator globin, is it not reasonable to expect similar action, to a lesser degree, when they are taken orally? If this is so, would there not be a greater possibility of arterial occlusion, particularly coronary, among the rank and file of women who are taking estrogens?*

M.D., California.

Answer.—The changes observed in the blood components that promote coagulation accompany the intravenous injection of relatively large amounts of the conjugated estrogens. This rapid increase in the estrogens seems to be essential. The continued oral administration, with slower gastrointestinal absorption, apparently does not have the same effect. Ancillary changes in capillary integrity, circulating lipids, and other elements involved in coagulation accompanying estrogen administration possibly protect the vascular system from the increased coagulability of the blood. Such an "explanation" for the lack of vascular disease in women taking estrogens is at present without complete experimental foundation. It is, however, known that purified components of the conjugated estrogens do not give rise to the same changes in coagulation components or to as great a degree if change does occur.

OPTIMUM HUMIDITY

To the Editor:—*What range of humidity is considered best for skin and mucous membranes? Has air-conditioning been known to reduce humidity to the point of inducing dermal or mucosal irritation?*

James H. Lade, M.D., Albany, N. Y.

Answer.—There are not sufficient scientific data at present to determine the humidity which is best for the skin and mucous membranes. Excessively low humidity, 20% or lower, causes drying of the skin and mucosa with decreased activity of the cilia lining the upper respiratory tract. Excessively high humidity may give an uncomfortable sensation and in warm weather interferes with heat loss. In cold weather any type of heating system or air-conditioning without accompanying humidification may give a low humidity, but any irritation of the skin and mucosa would be due entirely to the drying effect. In warm weather low humidity is not likely to occur with air-conditioning because dehumidification is expensive.

FUEL OIL DERMATITIS AND SEQUELAE

To the Editor:—*A 35-year-old pregnant woman, finding her basement floor flooded with fuel oil which had escaped from the tank, removed her hose and shoes and waded across the floor to turn off the valve and then proceeded, still barefoot, to clean up the basement. During the night she developed a massive macular eruption on her feet and ankles which was pruritic and burning. The next morning she discovered that she was unable to void, and she did not void until catheterization was done in the mid-morning. The urine at that time was almost milky in color and contained a few red blood cells, much mucus, many casts, and many leukocytes. After this she voided with difficulty because of tenesmus and dysuria which persisted until medication, which had been prescribed, became effective within 24 hours. Six days later she began to develop lower abdominal cramps which she said were like mild labor pains. In 48 hours she began to show some spotty uterine bleeding, and at the end of five days she had an abortion of an 8-week-old fetus. It is thought that the dermatitis was due to contact with the fuel oil and assumed that the urinary symptoms were due to the absorption or inhalation of some of the hydrocarbons in the fuel oil. May it be said that the abortion was also due to the toxic effects of the fuel oil?*

L. Mason Lyons, M.D., Terre Haute, Ind.

Answer.—In general, it can be said that there are no components of fuel oil which will cause all of the pathological changes observed in this patient. The occurrence of dermatitis after contact with fuel oil and its specific localization to the exposed portions of the body is rather conclusive evidence that some constituent of the fuel oil was the etiological agent, although two factors—the "massive macular eruption" and its appearance almost immediately after exposure—are not characteristic

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

of the usual dermatitides due to fuel oil. The patient's symptoms and urinary findings present a confused picture: the tenesmus, dysuria, mucus, and cellular elements indicate a cystitis, whereas the many casts show some renal involvement. The milky color of the urine requires more data for explanation, and no information is given regarding a febrile reaction or the presence of systemic symptoms. An abortion occurred one to two weeks after exposure and supposedly after all the dermal and urinary manifestations had subsided. No other associated systemic symptoms are given. Apparently this patient had no signs or symptoms referable to the central nervous, respiratory, or gastrointestinal systems, and some would certainly be expected if there had been inhalation of a volatile material or absorption through the skin of almost any known toxin. The components of fuel oil are not known to cause any of the pathological changes in the urinary or genital tract which occurred in this patient, nor is there any additive or solvent which would produce them. Therefore, while it seems more than likely that the dermatitis was due to the fuel oil, the rest of the patient's difficulties cannot be explained on the same basis and it is not clear why they occurred.

SIDE ACHE

To the Editor:—*What is the cause of the pain commonly experienced in the flank or upper part of the abdomen during strenuous exercise or rapid walking? An 18-year-old boy is unable to play basketball because of pain in the upper part of the abdomen which occurs only during exertion and which is relieved promptly by rest. Studies, including electrocardiogram, complete gastrointestinal series, and sickle cell preparations, all give negative findings. What treatment is recommended?*

M.D., Kentucky.

Answer.—The differential diagnosis of stabbing pains in the chest was considered by Langley (*Ann. West. Med. & Surg.* **6**:49, 1952). He listed a number of conditions in the thoracic viscera, thoracic wall, vertebral column, and abdominal viscera and mentioned the common "stitch in the side" or "side ache" about which many young people complain when running. He ascribed it to "strain of an intercostal muscle," but this explanation is given without evidence. Observations on 114 attacks of side ache in 55 persons were reported by Capps (*J. A. M. A.* **116**:2431 [May 24] 1941). The important features were found to be a constant relation to exertion, a tendency for the ache to occur after eating, a variable location, usually in either the right or the left upper quadrant of the abdomen, relief by bending over or from local pressure, and a tendency to aggravation in cold weather. Previously proposed theories regarding the mechanism of pain are untenable. Anoxemia of the diaphragmatic muscle for the side ache is the explanation offered. Why the pain is unilateral is not clear. Perhaps the person stops exercising before the other side begins to hurt. Improved breathing might well put less of a load on the diaphragm. There are theoretical reasons for supposing that recently introduced muscle-relaxant drugs might reduce the tendency of the diaphragm and intercostal muscles to go into spasms and that one or another of the many vasodilators now available might prevent ischemic contractions of these muscles. As yet, however, no studies along these lines have appeared.

INFECTIOUS HEPATITIS AND PREGNANCY

To the Editor:—*Are pregnant women less susceptible to infectious hepatitis than the rest of the population? Is this disease more benign in pregnant as compared to nonpregnant women? If pregnant women are not less susceptible to infectious hepatitis, should they receive gamma globulin for their own protection and for the protection of the fetus?*

Bertrand M. Bell, M.D., Donaldson, S. C.

Answer.—There is no evidence that pregnant women are less susceptible to infectious hepatitis than the rest of the population. Pregnancy places a greater strain on the liver, and infectious hepatitis in pregnancy is more dangerous not only for the mother but also for the fetus. If pregnant women are exposed to infectious hepatitis, gamma globulin should be given for protection of both mother and fetus. An intramuscular injection of about 0.02 ml. per pound of body weight would be suitable.

BLOOD SUGAR DETERMINATIONS

To the Editor:—*A newly employed, well-trained, registered technician has insisted on the use of what is called the dextrose-kit method of performing the blood sugar test. He maintains that this is as accurate as the older Folin-Wu method. Is he right?*

M.D., Alabama.

Answer.—The answer to this problem depends to a certain extent on which dextrose-kit method is used. There are several so-called dextrose-kit methods in which no colorimeter is required. The final color in the blood test is compared with color standards until a match is obtained. For example, one such test is based on the ferricyanide method of Folin. Color standards are set up in milligrams per 100 cc., and the results are accurate within about 10 mg. per 100 cc. of blood. Another method is based on the reduction of copper sulfate (Folin). The resulting color is matched against a color scale with 50-mg. intervals. The colors are much like those produced with Benedict's solution when used to test the urine for sugar. With this method, there

is a wide range in the accuracy of the reading. With any of these tests, no appreciable time is saved as compared with the standard blood sugar methods with use of a regular colorimeter. With all these methods, the blood needs to be precipitated and filtered. The filtrate, when mixed with the appropriate chemicals, is boiled for a given period. Consequently, no appreciable time is saved. Any physician who employs a medical technician should use a standard method with a regular colorimeter to obtain an accurate blood sugar level reading.

KOILONYCHIA

To the Editor:—*What is the treatment of koilonychia which has developed spontaneously in a 63-year-old woman? She first developed spooning of her fingernails two years ago, and it has progressed to involve all of the fingernails and has begun to involve the toenails as well. She has taken gelatin faithfully for over a year without any effect. Even though she was not anemic iron was given by mouth, without benefit. In the hope of producing some favorable effect, one physician prescribed large doses of the vitamins A, B, and C, as well as calcium tablets. These agents were given for three months, and no improvement was noted. The patient's basal metabolic rate and plasma cholesterol level are normal. Are any systemic diseases known to be associated with this condition?*

M.D., Ohio.

Answer.—Koilonychia still remains a real therapeutic problem in many instances. It may affect several fingers or all fingers at the same time, though very rarely. While it is common in some families, in others it occurs individually. It has been found to coexist with lichen planus, occasionally with other rare skin diseases, in extreme cachexia, and, rarely, with syphilis. On the other hand, it is often difficult, if not impossible, to determine the etiological agent. Several observers, such as Cipollaro, believe that many of these are occupational in origin, i. e., that they result from handling strong acids and alkalies, but others have not found this to be an important factor. A few cases have been associated with dystrophy of the hair and plantar and palmar hyperkeratoses. In some of these patients, vitamins A and D and calcium have been of help. In a few patients there has been an achlorhydric anemia which responded to appropriate iron medication, but there appears to be no such connection in the case in question. In this instance, apparently no cutaneous or internal abnormalities have been found. It would be justifiable to use vitamin D and calcium salts, the latter in the form of calcium gluconate given intramuscularly.

HYPERSENSITIVE DENTIN

To the Editor:—*About a year ago, information was obtained for the treatment of hypersensitive dentin. This included use of ammoniated silver nitrate, followed by 1 drop of eugenol, and brushing the teeth with hot mineral oil, Andresen's paste, sodium silicofluoride, or Thermodent tooth paste. A sodium fluoride-kaolin-glycerin mixture and stannous fluoride were not recommended because they might cause degeneration of the dental pulp. Is any other treatment recommended?*

M.D., West Virginia.

Answer.—All methods named have their enthusiastic proponents, but controlled clinical studies to support them are generally lacking. The sodium fluoride-kaolin-glycerin mixture has been adequately tested and shown to be an effective desensitizer. It can be used safely because damage to pulp results only when sodium fluoride is used in freshly cut cavities and, therefore, does not apply to desensitizing applications. Except for the fact that stannous fluoride and silver nitrate may stain teeth, they are perfectly safe. Desensitizing agents will not prevent recurrence of sensitivity if erosion is continuing and exposing fresh, sensitive dentin. Treatment should include correction of factors causing erosion or gingival caries. Andresen's paste, which is a mixture of phosphates and other salts, for daily application, is supposed to do this, but the evidence is unconvincing.

PHENOL FOR RHEUMATISM

To the Editor:—*Many people in this area use phenol as a sort of home remedy in the treatment of rheumatism, arthritis, and allied diseases. The usual dose is one drop, diluted with water, taken three times a day. Good results are claimed. Would this be safe over a prolonged period?*

M.D., Missouri.

Answer.—There appears to be no therapeutic rationale for the administration by mouth of phenol in any form of arthritis. This consultant would advise against it.

"AIR PLATES" AND CONTROL OF HOSPITAL INFECTIONS

To the Editor:—*A more satisfying answer to the question on "air plates" and control of hospital infections, published in* The Journal, *Dec. 27, 1958, page 2329, can be found by perusal of the book by Wells (Airborne Contagion and Air Hygiene, Cambridge, Mass., Harvard University Press, 1955). Briefly, a 15-minute exposure of a Petri dish represents the number of particles settling out on 1 sq. ft. per minute (rate of deposit). Volume air samplers collect the total number of bacteria in a given volume (bacterial*

density). Settling velocity is the quotient. A high settling velocity (greater than 1) indicates dustborne bacteria and a low velocity, droplet nuclei (less than 4 ft. per minute). Room air has a settling velocity of 1 or 2 ft. per minute, indicating the preponderance of dustborne organisms. Settling velocities can be used to differentiate airborne from dustborne contagion.

Carl W. Walter, M.D.
Peter Bent Brigham Hospital
721 Huntington Ave.
Boston 15.

AEROPHAGIA

To the Editor:—*In* The Journal, *Nov. 22, 1958, page 1734, in answer to a question on aerophagia the consultant suggested eating with the mouth closed as a preventive measure. While it is true that this may help, much of the swallowed air enters the esophagus through the nose rather than the mouth. To prevent this, some form of nasal pinchers, such as those used in underwater training of lifeguards, would be helpful, or small cotton pledgets moistened with water might be placed in each nostril. Charcoal is of doubtful value because a very large quantity would be required to absorb all the air in the stomach. Furthermore, charcoal loses its ability to absorb gases when it is wet.*

G. Franco Capuani, M.D.
Bal. Lamarmora, 15
Novara, Italy.

The above comment was referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*It will rarely be necessary for persons with aerophagia to use pinchers or pledgets of moist cotton to close their nose when swallowing. This would be quite impractical, if not impossible. Furthermore, when the nose is closed, a person takes in air through his mouth. It is not clear just how charcoal works in a situation like this. From our clinical experience, however, it definitely reduces the amount of intestinal gas and it has been thought to do so by absorption. Many persons get striking relief from gaseous dyspepsia by this simple procedure.*

URIC ACID AND PREECLAMPSIA

To the Editor:—*In regard to the question on uric acid and preeclampsia, which appeared in* The Journal, *Feb. 14, 1959, page 777, it may be relevant to point out that chlorothiazide may raise the serum uric acid level (Laragh and others,* J. A. M. A. **166:***145-152 [Jan. 11] 1958; Oren and others,* J. A. M. A. **168:***2128-2129 [Dec. 20] 1958). Chlorothiazide is often given to patients with toxemia of pregnancy. Currently, at Cook County Hospital, work being done on this subject seems to indicate that when chlorothiazide is given in doses of 0.5 Gm. twice daily a slight increase in the serum uric acid level occurs in pregnant patients with and without toxemia. Perhaps the inquiring physician used larger doses. The hyperuricemic effect of chlorothiazide may be important if one relies on the uric acid level for prognosis or treatment.*

Irving Siegel, M.D.
5054 N. St. Louis Ave.
Chicago 25.

BLOOD PRESSURE DETERMINATION AND VALVULAR DISEASE OF THE HEART

To the Editor:—*In the Jan. 10, 1959, issue of* The Journal, *page 202, a question appeared concerning the "sea gull murmur," described as a high-pitched systolic murmur; the consultant indicated this is a "high-pitched, screeching systolic murmur maximal near the cardiac apex." The information which is available to me on this subject is somewhat at variance with these opinions. According to Groom and Boone (*Ann. Int. Med. **42:***1214, 1955), the sea gull murmur, also known as the "dove-coo" murmur, is a unique musical murmur, decrescendo in character, prolonged through most of diastole, and generally maximal in the mid-precordium. The consultant indicated that most of these murmurs have been shown to be associated with eversion or retroversion of an aortic valve cusp, usually from syphilitic aortitis.*

George X. Trimble, M.D.
Seaside Memorial Hospital
1401 Chestnut Ave.
Long Beach, Calif.

The above comment was referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*The comment relative to the sea gull murmur is appropriate if it is based on the article by Groom and Boone, because in that article the sea gull murmur is described as synonymous with the dove-coo murmur. This consultant knows of no authoritative source to indicate that a sea gull murmur has specific diagnostic value. By common usage it has come to mean a high-pitched, musical, screeching murmur, and most of these are systolic in time, in contrast to a similar musical murmur, diastolic in time, which may be specifically related to aortic insufficiency. This seems to be a matter of semantics which does not have a firm traditional foundation.*

Louis Orr

PRESIDENT-ELECT, AMERICAN MEDICAL ASSOCIATION, 1958-1959

RUFUS B. ROBINS
Camden, Ark.

W. LINWOOD BALL
Richmond, Va.

JAMES Z. APPEL
Lancaster, Pa.

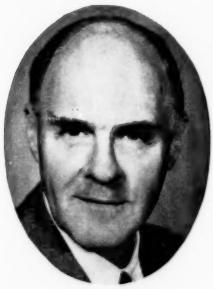
JULIAN P. PRICE
Florence, S. C.

LEONARD W. LARSON
Bismarck, N. D.
Chairman

HUGH H. HUSSEY JR.
Washington, D. C.
Secretary

GEORGE M. FISTER
Ogden, Utah

CLEON A. NAFE
Indianapolis



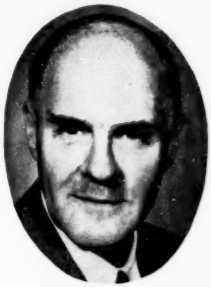
RAYMOND M. McKEOWN
Coos Bay, Ore.

THE PRESIDENT AND THE PRESIDENT-ELECT ALSO ARE MEMBERS OF THE BOARD OF TRUSTEES

BOARD OF TRUSTEES

E. VINCENT ASKEY
Los Angeles
Speaker

W. LINWOOD BALL
Richmond, Va.
Vice-President



RAYMOND M. McKEOWN
Coos Bay, Ore.
Secretary-Treasurer

NORMAN WELCH
Boston
Vice-Speaker

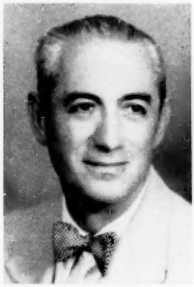
GUNNAR GUNDERSEN
LaCrosse, Wis.
President 1958-1959

F. J. L. BLASINGAME
Chicago
Executive Vice-President

OFFICERS

JOHN ADRIANI
New Orleans
Chairman
Section on Anesthesiology

CLARENCE S. LIVINGOOD
Detroit
Chairman
Section on Dermatology



M. JAY FLIPSE
Miami
Chairman
Section on Diseases of the Chest

CHARLES H. BURNETT
Chapel Hill, N. C.
Chairman
Section on Experimental Medicine
and Therapeutics

A. W. MARTIN MARINO
Brooklyn, N. Y.
Chairman
Section on Gastroenterology
and Proctology

S. A. GARLAN
New York
Chairman
Section on General Practice

WILLIAM B. BEAN
Iowa City
Chairman
Section on Internal Medicine

VICTOR R. ALFARO
Washington, D. C.
Chairman
Section on Laryngology, Otology
and Rhinology

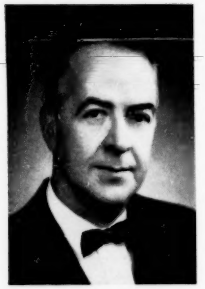
ALPHONSE McMAHON
St. Louis
Chairman
Section on Military Medicine

KENNETH E. APPEL
Philadelphia
Chairman
Section on Nervous and
Mental Diseases

NICHOLSON J. EASTMAN
Baltimore
Chairman
Section on Obstetrics and Gynecology

FRANK B. WALSH
Baltimore
Chairman
Section on Ophthalmology

LENOX D. BAKER
Durham, N. C.
Chairman
Section on Orthopedic Surgery



THOMAS M. PEERY
Washington, D. C.
Chairman
Section on Pathology and Physiology

WYMAN C. C. COLE Sr.
Detroit
Chairman
Section on Pediatrics

ARTHUR L. WATKINS
Boston
Chairman
Section on Physical Medicine

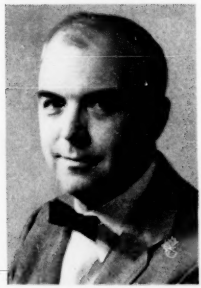
ROBERT A. KEHOE
Cincinnati
Chairman
Section on Preventive Medicine

TED F. LEIGH
Atlanta, Ga.
Chairman
Section on Radiology

JOHN H. MULHOLLAND
New York
Chairman
Section on Surgery, General and Abdominal

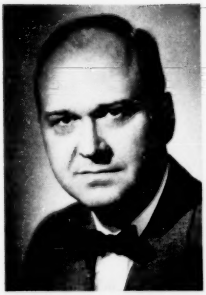
MILTON M. COPLAN
Miami
Chairman
Section on Urology

VINCENT J. COLLINS
New York
Secretary
Section on Anesthesiology

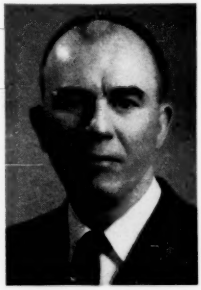


EDWARD P. CAWLEY
Charlottesville, Va.
Secretary
Section on Dermatology

BURGESS L. GORDON
Albuquerque, N. Mex.
Secretary
Section on Diseases of the Chest



ELLIOT V. NEWMAN
Nashville, Tenn.
Secretary
Section on Experimental Medicine and Therapeutics



WILLIAM H. DEARING
Rochester, Minn.
Secretary
Section on Gastroenterology and Proctology

E. I. BAUMGARTNER
Oakland, Md.
Secretary
Section on General Practice

RUDOLPH H. KAMPMEIER
Nashville, Tenn.
Secretary
Section on Internal Medicine

WALTER E. HECK
San Francisco
Secretary
Section on Laryngology, Otology and Rhinology

CHARLES H. BRAMLITT
Washington, D. C.
Secretary
Section on Military Medicine

A. L. SAHS
Iowa City
Secretary
Section on Nervous and Mental Diseases

KEITH P. RUSSELL
Los Angeles
Secretary
Section on Obstetrics and Gynecology

HAROLD G. SCHEIE
Philadelphia
Secretary
Section on Ophthalmology

ROBERT J. JOPLIN
Brookline, Mass.
Secretary
Section on Orthopedic Surgery

HUGH A. EDMONSON
Los Angeles
Secretary
Section on Pathology and Physiology

ARILD E. HANSEN
Galveston, Texas
Secretary
Section on Pediatrics

EARL C. ELKINS
Rochester, Minn.
Secretary
Section on Physical Medicine

FRANK PRINCI
Cincinnati
Secretary
Section on Preventive Medicine

TRAIAN LEUCUTIA
Detroit
Secretary
Section on Radiology

GUSTAF E. LINDSKOG
New Haven, Conn.
Secretary
Section on Surgery, General and Abdominal

EDWARD H. RAY
Lexington, Ky.
Secretary
Section on Urology